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(54) THERAPEUTIC COMPOSITIONS AND METHODS

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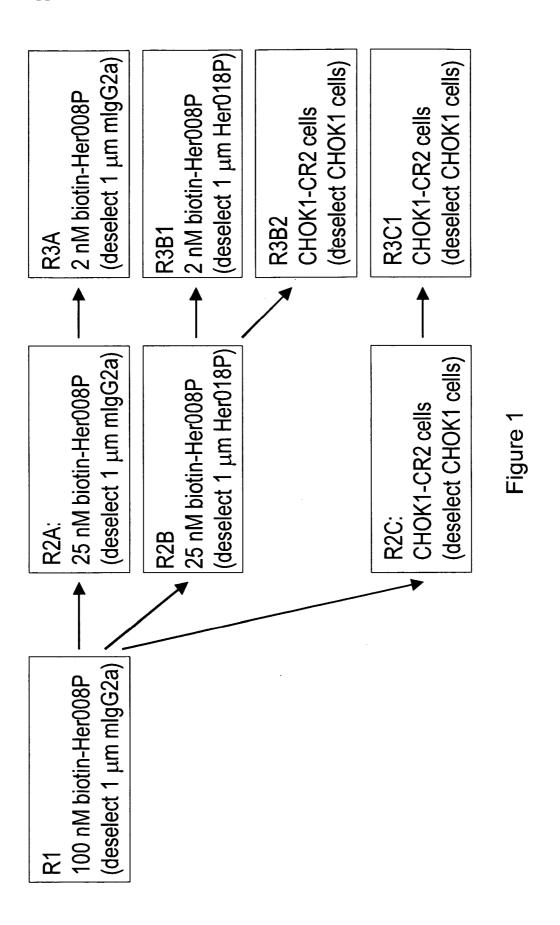
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(57) **ABSTRACT**

The present application provides novel binding proteins, including human binding proteins that specifically bind to the human ErbB2.



FW 1CDR 24QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYNGNTNYAQKLQG2QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYNGNTNYAQKLQG4EVQLVQSGAEVKEPGASVKVSCKASGYDFSNYGFSWVRQAPGQGLEWMGWISSYNGYTNYAQKLQG	 FW 3 RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	Figure 2A	 FW 1 CDR 1 FW 2 CDR 2 QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYAMHWVRQAPGQRLEWMGWINAGNGNTKYSQKFQG QVQLVESGAEVKKPGASVKVSCKASGYTFTSYDINWVRQAPGQRLEWMGWINAGNGNTKYSQKFQG 	FW 3 CDR 3 FW 4 25 RVTITRDTSASTAYMELSSLRSEDTAVYYCAR
VH1_DP14 S1R3B2_BMV_1G2 S1R3B1_BMV_1A1	VH1_DP14 S1R3B2_BMV_1G2 S1R3B1_BMV_1A1		VH1_DP25 S1R3A1_BMV_1G4	VH1_DP25 S1R3A1_BMV_1G4

Figure 2B

FW 1 CDR 1 FW 2 VH3_DP47 EVQLLESGGGLVQFGGSLRLSCAASGFFFSSYAMSWVRQAFGKGLI S1R3B2_DP47_1H3 EVQLLESGGGLVQFGGSLRLSCAASGFFFSSYAMSWVRQAFGKGLI S1R3B2_DP47_1E1 EVQLLESGGGLVQFGGSLRLSCAASGFFFSSYAMSWVRQAFGKGLI S1R3B2_DP47_1E1 EVQLLESGGGLVQFGGSLRLSCAASGFFFSSYAMSWVRQAFGKGLI S1R3B2_DP47_1E1 EVQLLESGGGLVQFGGSLRLSCAASGFFFSSYAMSWVRQAFGKGLI S1R3B2_DP47_1E1 EVQLLESGGGLVQFGGSLRLSCAASGFFFSSYAMSWVRQAFGKGLI S1R3B2_DP47_1E1 EVQLLESGGGLVQFGGSLRLSCAASGFFFSSYAMSWVRQAFGKGLI S1R3B1_DP47_1E1 EVQLLESGGGLVQFGGSLRLSCAASGFFFSSYAMSWVRQAFGKGLI S1R3B1_DP47_1E1 EVQLLESGGGLVQFGGSLRLSCAASGFFFSSYAMSWVRQAFGKGLI S1R3B2_DP47_1E1 EFTISRDNSKNTLYLQMNSLRAEDTAVYCGAKWRPLLDYHF S1R3B2_DP47_1E1 EFTISRDNSKNTLYLQMNSLRAEDTAVYCGAKGSGSGADWFFF S1R3B1_DP47_1E1 EFTISRDNSKNTLYLQMNSLRAEDTAVYCGAKGSGSGADWFFFF S1R3B1_DP47_1E1 EFTISRDNSKNTLYLQMNSLRAEDTAVYCGARGSGSGSGADWFFFF S1R3B1_DP47_1E1 EFTISRDNSKNTLYLQMNSLRAEDTAVYCGARGGSGSGSGGGGGGSGSGADWFFFF
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Figure 2D

1_VH_Her2_S1_pileup_17843.txt MSF: 124 Type: P May 21, 2007 16:01 Check: 413
Name: 1_VH_Her2_S1R2A_CS_1D11 Len: 124 Check: 7283 Weight: 1.00 Name: 1_VH_Her2_S1R2C_CS_1D3 Len: 124 Check: 7153 Weight: 1.00 Name: 1_VH_Her2_S1R3C1_CS_1B10 Len: 124 Check: 5945 Weight: 1.00 Name: VH1_DP10_germline Len: 124 Check: 32 Weight: 1.00
// 1 50 1_VH_Her2_S1 EVQLVQSGSE VRRPGSSVRV SCTASGDTSS SFTVNWLRQA PGQGLEWMGG 1_VH_Her2_S1 QVQLVQSGSE VRRPGSSVRI SCTASGDTSS SFTVNWVRQA PGQGLEWMGG 1_VH_Her2_S1 QVQLQQSGAE VKKPGSSVKV SCKASGGTIS NYAISWVRLA PGQGLEWMGS VH1_DP10_ger QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGS
51 1_VH_Her2_S1 ITPMFGTANY AQMFEDRVTI TADE MELSGLTSED TAVYFCATGP 1_VH_Her2_S1 ITPMFGTANY AQVFEDRVTI IADE MELSGLTSED TAVYFCATGP 1_VH_Her2_S1 IVPLHGTTNF AQKFQGRVTI TADESTSTSY MEVNVLTYED TAMYYCASLN VH1_DP10_ger IIPIFGTANY AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCAR~~
101 1_VH_Her2_S1 SDYVWGSYRF LDTWGRGTTV TVSS 1_VH_Her2_S1 SDYVWGSYRF LDRWGRGTLV TVSS 1_VH_Her2_S1 WGYWGRGTLV TVSS VH1_DP10_ger ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
Figure 2E

 FW 1 CDR 1 FW 2 CDR 2 QVQLQQSGFGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYAVSVKS QVQLQESGFGLVKPSQTLSLTCGISGDSVSSNSAAWNWIRQSPTRGLEWLGRTYYRSSWYHNYAPSMNSR 	<pre>FW 3 CDR 3 FW 4 74 RITINPDTSKNQFSLQLNSVTPEDTAVYYCAR</pre>	Figure 2F	FW 1 CDR 1 FW 2 CDR 2	 T3 EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWURQMPGKGLEWMGIIYPGDSDTRYSPSFQG A6 EVQLVQSGAEVKKPGESLKISCKGFGYNFRSAWIGWURQMPGKGLEWMGVIYPGDSDVRYSPSFQG B9 KVQLVQSGTEVKKPGESLKISCQGSGYRFSSDWIAWURQMPGKGLEWMGIIYPGDSDTRYSPSFQG 11 EVQLVQSGAEVKKPGESLKISCKGSGYTFTNHWIAWURQMPGKGLEWMGIIYPGDSETRYSPSFQG 	 FW 3 CDR 3 CDR 3 CDR 3 PW 4 23 QVTISADKSISTAYLQWSSLKASDTAMYYCAR. GVTISADKSISTAYLQWSSLKASDTAMYYCTRPVGQWVDSDYWGKGTLVTVSS. B9 QVTISADKSISTAYLQWSGLKASDTAKYYCARVQQAVGAKGYAMDVWGKGTLVTVSS. 11
VH6_DP74 S1R3C1_CS_1D3	VH6_DP74 S1R3C1_CS_1D3			VH5_DP73 S1R3C1_CS_1A6 S1R3A1_CS_1B9 S1R3A1_CS_1D11 S1R3A1_CS_1D11	VH5_DP73 S1R3C1_CS_1A6 S1R3A1_CS_1B9 S1R3A1_CS_1D11 S1R3A1_CS_1D11

Figure 2G

CDR 1 FW 2 CDR 2 NWWSWVRQPPGKGLEWIGEIYHSGSTNYNPSLKS NWWSWVRQPPGKGLEWIGEISHSGSTNYNPSLKS	CDR 3 FW 4	H	
FW 1 CDR 1 FW 2 QVQLQESGPGLVKPSGTLSLTCAVSGGSISSSNWWSWVRQPPGKGLEWIGEIY- QVQLQESGAGLVKPSGTLSLTCAVSGGSISSGNWWSWVRQPPGKGLEWIGEIS-	FW 3 CDR 3 RVTISVDKSKNQFSLKLSSVTAADTAVYYCAR	Figure 2H	
VH4_DP70 S1R3B1_BMV_1H9	VH4_DP70 S1R3B1_BMV_1H9		

VH3_DP77 S1R3A1_BMV_1F3	FW 1 EVQLVESGGGLVKPGGSLRLSCAASGFTFS S EVQLVESGEGLVKPGGSLRLSCTASGFTFR S	CDR 1 YSMNWV YSLNWV	FW 1 CDR 2 CDR 2 CDR 2 CDR 2 PGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYIYYADSVKG PGGSLRLSCTASGFTFRSYSLNWVRQAPGQGLEWVSSISSTSTYIYYADSVKG	CDR 2 sssyiyyAdsvkg tstyiyyAdsvkg
VH3_DP77	FW 3 CDR 3 FW 4	CAR	FW 3 CDR 3 FW 4	FW 4
S1R3A1_BMV_1F3	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR		YLQMNSLRAEDTAVYYCAR	

Figure 2I

FW1 CDR1 FW2 CDR2 VH3_DP51 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSYISSSGNTIFYADSVKG EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYGMNWVRQAPGKGLEWVSYISSSGNTIFYADSVKG S1R2C_CS_1H12 EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYGMNWVRQAPGKGLEWVSYISSSGNTIFYADSVKG CDR3 FW4 VH3_DP51 FW3 CDR3 FW4 Image: CDR3 FW4 NH3_DP51 RFTISRDNAKNSLVLQMNSLRDEDTAVYYCAR	FW 1CDR 1FW 2CDR 2VH3_DP50QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGS1R3B1_BWV_1H1EVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAGIFYDGSNKYYADSVKGS1R3B1_BMV_1H1EVQLVETGGGVVQPGGSLSLSCAASGFTFSSYGMHWVRQAPGKGLEWVAGIFYDGSNKYYADSVKGS1R3B1_BWV_1H5EVQLVESGGGVVQPGGSLSLSCAASGFTFSSYGMHWVRQAPGKGLEWVAGIFYDGSNKYYADSVKGS1R3B1_BMV_1H5EVQLVESGGGVVQPGGSLSLSCAASGFTFSSYGMPWVRQAPGKGLEWVAKIRYDGSSKYYADSVKGS1R3B2_BWV_1H5EVQLVQSGGGLVRPGGSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAKINNDGSSKYYADSVKGS1R3B2_BMV_1H5EVQLVQSGGGLVRPGGSLRLSCAASGFFFSSYMMTWVRQAPGKGLEWVAKINNDGSSKYYADSVKGS1R3B2_BVK	FW 3CDR 3FW 4VH3_DP50RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	VH3_DP51 S1R2C_CS_1H12 VH3_DP51 S1R2C_CS_1H12 S1R2C_CS_1H12 S1R3B1_BMV_1H11 S1R3B1_BMV_1H5 S1R3B1_BMV_1H5 S1R3B1_BMV_1H5 S1R3B1_BMV_1H5 S1R3B1_BMV_1H5 S1R3B1_BMV_1H5 S1R3B1_BMV_1H5 S1R3B1_BMV_1H5 S1R3B1_BMV_1H5 S1R3B1_BMV_1H5	FW 1 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYG EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYG FW 3 RFTISRDNAKNSLYLQMNSLRDEDTAVYYCA RFTISRDSAKNSVSLQMNSLRDEDTAVYYCA FW 1 Pigure FW 1 Pigure FW 1 QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYG EVQLVESGGGVVQPGGSLRLSCAASGFTFSSYG QVQLVESGGGVVQPGGSLRLSCAASGFTFSSYG EVQLVQSGGGLVRPGGSLRLSCAASGFTFSSYG QVQLVESGGGVVQPGGSLRLSCAASGFTFSSYG EVQLVQSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVQSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVQSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVQSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVQSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVQSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVQSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVCSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVCSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVCSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVCSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGSSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGSSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGSSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGSSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGSSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGSSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGSSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGSSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGSSLRLSCAASGFTFSSYG FVG EVQLVSSGGGLVRPGSSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGLVRPGGSLRLSCAASGFTFSSYG EVQLVSSGGGVVSP EVQLVSSCAASGFTFSCAASGFTFYG EVQLVSSGGGVVCP EVQLVSSGGGLVRP EVQLVSSCAASGFTFS EVQLVF EVQLVSSCAASGGGLVRP EVQLVSSCAASGFTFS EVQLVVCSGGGLVRP EVQLVSSCAASGFTFS EVQLVVC EVQLVSCAASCAASCFTFS EVQLVVC EVQLVSSCAASGGCVVCP EVQLVSCAASCFTFS EVQLVSCAASCFTFF EVQLVVC EVQLVSCAASCGCVVCP EVQLVC EVQLVSCAASCFTF EVQLVVC EVQLVC EVQLVC EVQLVC EVQLVC EVQLVC EVQLVC EVQLVC EVQLVC EVQLVC EVQLV EVC EVQLV EVQLVC EVQLV EVC EVC EVC EVC	CDR 1 FW 2 SMNWURQAPGKGLE SMNWURQAPGKGLE SMNWURQAPGKGLE ASYYSYYY	CDR 2 WV SYISSSGNTIFYADSVKG WV SYISSSGNTIFYADSVKG FW 4 GMDAWGQGTMVTV. GMDAWGQGTMVTV. GMDAWGQGTMVTV. GMDAWGQGTMVTV. GMDAWGQGTMVTV.
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Figure 2K

FW 1 CDR 2 CDR 1 FW 2 CDR 2 CDR 2 QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKG EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSIKYYADSVKG QMQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSIKYYADSVKG	FW 3 FW 3 FW 3 FW 3 FW 5 FW 5 FW 5 FW 1 FW 1 FW 1 FW 1 FT ISRDNSKNTLYLQMNSLRAEDTAVYYCAK	Figure 2L	FW 1 CDR 2 CDR 2 CDR 1 FW 2 CDR 2 VOLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPNSGGTNYAQKFQGW EVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPNSGGTNYAQKFQGW QVQLVQSGAEVKKPGASVKVSCQASGYTFSGHYMHLVRQAPGQGLEWMGWIHPTSGGTTYAQKFQG EVQLVQSGAEVKKPGASVKVSCKASGYSFTAFYIHWVRQAPGQGLEVMGWIHPNTGATKYAQKFQG	FW 3 VTMTRDTSISTAYMELSRLRSDDTAVYYCAR
VH3_DP49 S1R3B1_BMV_1C12 S1R3B1_BMV_1A10	VH3_DP49 S1R3B1_BMV_1C12 S1R3B1_BMV_1A10		VH1_DP8 S1R2A_CS_1F7_1 S1R3A1_CS_1B12 S1R2A_CS_1D3_1 S1R2A_CS_1D3_1 S1R3A1_CS_1B10	VH1_DP8 S1R2A_CS_1F7_1 S1R3A1_CS_1B12 S1R2A_CS_1B12 S1R3A1_CS_1B10 S1R3A1_CS_1B10

Figure 2M

VK1_L12 S1R3B2_BMV_1G2	FW 1 DIQMTQSPSTLSASVGDRVTITC RASQ DIQMTQSPSTLSASIGDRVTITC RASE	СDR 1 SISSWLAWYQQ ¹ GIYHWLA WYQQ1	CDR 1 FW 2 CDR 2 SISSWLAWYQQKPGKAPKLLIYKASSLES GIYHWLAWYQQKPGKAPKLLIYKASSLAS	SLES SLAS
VK1_L12 S1R3B2_BMV_1G2	S S H	SLQPDDFATYYCQQYN		
	Figure 3A	3A		
	FW 1	CDR 1	FW 2 CDR 2	
VK1_L12 S1R3C1_BMV_1H11	DIQMTQSPSTLSASVGDRVTITC RASQ DIQMTQSPSTLSASIGDRVTITC RASE	SISSWLAWYQQKPGKAPKLLIY KA GIYHWLAWYQQKPGKAPKLLIY KA GIYHWLAWYQQKPGKAPKLLIY KA		SSLES SSLAS
	FW 3	CDR 3	FW 4	

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GVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYN.....

GAPSRFSGSGSGTDFTLTISSLQPDDFATYYCQQYSNYP----

VK1_L12 S1R3C1_BMV_1H11

FW 1 CDR 2 SVLTQPPS-ASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPS SYVLTQPPS-ASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPS QSVLTQPPS-ASGTPGQRVTISCSGSSSNIGTNTVNWYQQLPGTAPKLLIYTSNQRPS HVILTQPPS-ASGTPGQRVTISCSGSSSNIGTNTVNWYQQLPGTAPKLLIYTSNQRPS QSVLTQPPS-ASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLNYTNNQRPS QSVLTQPPS-ASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLNYTNDQRPS QSVLTQPPS-ASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLNYTNDQRPS	FW 3 GVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWD	Figure 3C	FW 1 CDR 1 FW 2 CDR 2 OT VT QEPS-FSVSPGGTVTLTCGLSSGSVSTSYYPSWYQQTPGQAPRTLIYSTNTRSS QAVVLQEPS-FSVSPGGTVTLTCGLRSGSVSTSHYPSWYQQTPGQAPRTLIYSTNTRSS QTVVLQEPS-FSVSPGGTVTLTCGLSSGSVSTSYYPSWYRQTPGQAPRTLIHNTKIRSS QTVVLQEPS-FSVSPGGTVTLTCGLSSGSVSTAYYPSWYRQTPGQAPRTLIYGTNIRSS QTVVLQEPS-FSVSPGGTVTLTCGLNFGSVSTAYYPSWYRQTPGQAPRTLIYGTNIRSS	FW 3 GVPDRFSGSILGNKAALTITGAQADDESDYYCVLYM	Figure 3D
VL1_DPL2 S1R2C_CS_1H12 S1R3C1_CS_1A6 S1R3A1_DP47_1A6 S1R3B1_BMV_1C12 S1R3B2_DP47_1C9	VL1_DPL2 S1R2C_CS_1H12 S1R3C1_CS_1A6 S1R3A1_DP47_1A6 S1R3B1_BMV_1C12 S1R3B2_DP47_1C9		VL8_DPL21 S1R3A1_CS_1D11 S1R3A1_CS_1B9 S1R3A1_CS_1B10 S1R3A1_CS_1B10	VL8_DPL21 S1R3A1_CS_1D11 S1R3A1_CS_1B9 S1R3A1_CS_1B10	

S1R3B1_BMV_1H9 S1R3A1_BMV_1F3 S1R3B1_BMV_1A10	SSELTQDPA-VSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS SSELTQDPA-VSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS SSELTQDPA-VSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS SSELTQDPA-VSVALGQTVRITCQGDSNNRPS	- VSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS - VSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS - VSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS
	FW 3	CDR 3 FW 4
VL3_DPL16	GIPDRFSGSSSGNTASLTITGAQAEDEADYYC NSRD	RD
S1R3B1_BMV_1H5	GIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHVVFGGGTKLTVLGA.	RDSSGNHVVFGGGTKLTVLGA.
S1R3B1_BMV_1H9	GIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHVVFGGGTKLTVLGA.	RDSSGNHL-VVFGGGTKLTVLGA.
S1R3A1_BMV_1F3	GIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHVVFGGGTKLTVLGA.	RDSSGNHLUVFGGGTKLTVLGA.
S1R3B1_BMV_1A10	GIPDRFSGSSSGNTASLTITGAQAEDEADYYCHS:	SSGNTASLTITGAQAEDEADYYCHSRDSSGNHVLFGGGTKLTVLGA.

Figure 3F

VL3_3h	FW 1 CL VSVAPGQTARITCGGNN	FW 2 CDR 2 IGSKSVHWYQQKPGQAPVLVVYDDSDRPS
S1R2A_CS_1F7_1 S1R3C1_DP47_1H1	QSVLTQPPS-VSVAPGQTARMTC GGNN QSVLTQPPS-VSVAPGQTARITC GGDK	IESKTVHWYQQKPGQAPVLVYNDNVRPS IGHKSVHWYQQKPGQAPVLLVYDDRKRPS
VL3_3h S1R2A_CS_1F7_1 S1R3C1_DP47_1H1	FW 3 CDR 3 GIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWD GIPARFSGSNSGNTATLTINRVEAGDEADYYCQVWDSSRDQ GIPERFSGSNSGNTATLTISRVEAGDEAAYHCQVWDRSSDP	FW 3 CDR 3 FW 4 SGNTATLTISRVEAGDEADYYCQVWD
	Figure 3G	
VL2_DPL11	FW 1CDR 1FW 2QSALTQPAS-VSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEV	FW 2 CDR 2 GGYNYVSWYQQHPGKAPKLMIYEVSNRPS
S1R3B1_BMV_1G11 S1R3A1_BMV_1G4	VSGSPGQSITISC TGTSSDV VSGSPGQSITISC TGTSSDV	GGYNYVSWYQQHPGKAPKLMIYEGSKRPS GGYNYVSWYQQHPGKAPKLMIYEGSKRPS
S1R3B1_BMV_1A1 S1R3B2_BMV_1H5	QSVLTQPAS-VSGSPGQSITISC TGTSSDV SSELTQPAS-VSGSPGQSITISC TGTSSDV	·VSGSPGQSITISC TGTSSDVSGYNYVS WYQQHPGKAPKLMIY EGSKRPS ·VSGSPGQSITISC TGTSSDVGGYNYVS WYLQHPGKAPKLMIY EGSKRPS
VL2_DPL11	FW 3 CDR 3 GVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYT	CDR 3 FW 4

Figure 3H

VL2_DPL11 S1R3B1_BMV_1G11 S1R3A1_BMV_1G4	FW 3 CDR 3 FW 4 GVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTTRSTRVFGGGTKLTVLGA. GVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTTRSTRVFGGGTKLTVLGA. GVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTTRSTRVFGGGTKLTVLGA.	CDR 3 FW 4 	FW 4 LTVLGA. LTVLGA.
S1R3B1_BMV_1A1	GVSNRFSGSKSGNTASLTISGLQAEDEADYYC SSYTTRST- -	:RSTRV FGGGTKLTVLGA.	LTVLGA.
S1R3B2_BMV_1H5	GVSNRFSGSKSGNTASLTISGLQAEDEADYYC SSYTTRST- -	:RSTRV FGGGTKLTVLGA.	LTVLGA.

	FW 1	CDR 1 FW 2	CDR 2
VL2_2c S1R3C1_CS_1D3	QSALTQPPS-ASGSPGQSVTISC TGTSSDV QSVLTQPPS-ASGSPGQSVTISC TGTSSDV	CTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEV CTGTSSDVGAYDFVSWYQQHPGKAPKLMIYEV	°KLMIY EVSKRPS °KLMIY EVNKRPS
VL2_2c S1R3C1_CS_1D3	FW 3 GVPDRFSGSKSGNTASLTVSGLQAEDEADYYC SSYA GVPDRFSGSKSGNTASLTVSGLQAEDEADYYC SSYAGSKN -	CDR 3	FW 4
	Figure 3I	31	
	EW 1	CDR 1 FW 2	CDR 2
VL1_DPL8 S1R3B1_BMV_1H11 S1R3A1_CS_1B12 S1R3B2_DP47_1E8	APGQRVTISC TGSSSNI APGQRVTISC TGRSSNI APGQRVTISC TGSSSNI APGQRVTISC TGTSSNI	GAGYDVHWYQQLF GAGHDVHWYQQLF GAGYDVNWYQQFF GTNYLVHWYQQRF	
	FW 3	CDR 3	FW 4
VL1_DPL8 S1R3B1_BMV_1H11 S1R3A1_CS_1B12	GVPDRFSGSKSGTSASLAITGLQAEDEADYYC QSYD GVPDRFSGSRSGTSASLAITGLQAEDEADYYC QSYDSSLRG GAPDRFSGSKSGTSASLAITGLRAEDEADYYC QSWDSRLSS	· ·	

Figure 3J

GVTDRFSVSKSATSASLAITGLQAEDEADYYCQ**TYDINLRV---**

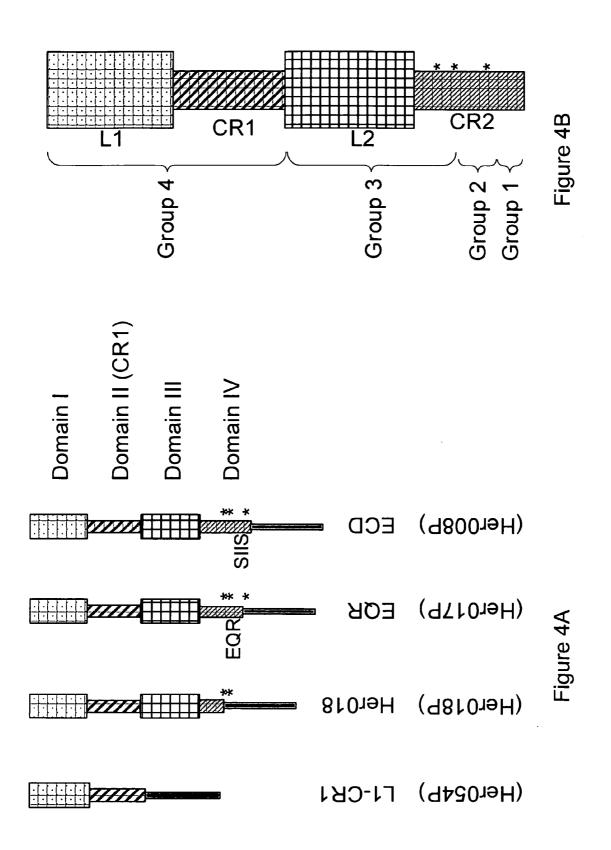
S1R3B2_DP47_1E8

--LGA.

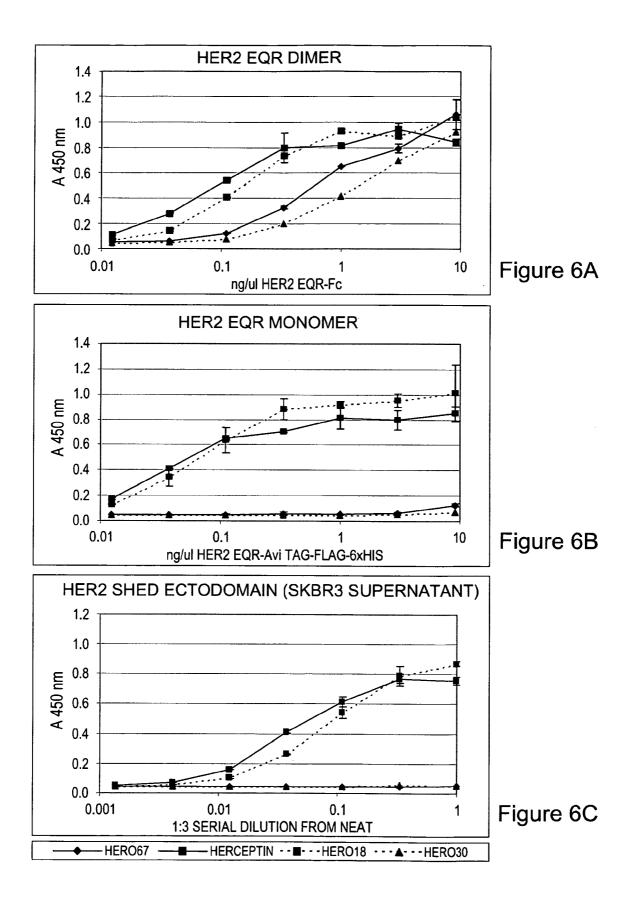
---WVFGGGTKVTV-

VL1_DPL5 S1R2C_CS_1D3 S1R2A_CS_1D11 S1R3B2_BMV_1E1	FW 1 CDR 2 CDR 1 FW 2 CDR 2 QSVLTQPPS-VSAAPGQKVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYDNNKRPS QSVLTQPPS-VSAAPGQKVTISCSGGRSSIGNNYVSWYQHLPGTAPKLLIYDNNQRPS QAVLTQPPS-VSAAPGQEVSISCSGGRSSNVGGNYVSWYQHLPGTAPKLLIYDNNRRPS QSVLTQPPS-VSAAPGQEVTISCSGSTSNIGNNYVSWYQHPGKAPKLMIYDVSKRPS
VL1_DPL5 S1R2C_CS_1D3 S1R2A_CS_1D11 S1R3B2_BMV_1E1	FW 3 CDR 3 FW 4 GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWD
	Figure 3K
VL1_DPL3	N 1 FW 2 sgtpgqrvtiscssssnigsnyvywyqqlpgtapKlliyrn
S1R2A_CS_1D3_1 S1R3B2_DP47_1E10	QSVLTQPPS-ASGTPGQRVTISC SGSSSNIGSNYVY WYQQLPGTAPKLLIY RNNQRPS HVILTQPPS-TSGTPGQTVTISC SGSSSNIGSHYVY WYQQLPGTAPKLLIY RNNQRPS
VL1_DPL3 S1R2A_CS_1D3_1 S1R3B2_DP47_1E10	FW 3 CDR 3 FW 4 FW 3 CDR 3 FW 4 GVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWD

Figure 3L



		ScFv ON PH	SCFV ON PHAGE BINDING TO CELLS	TO CELLS	ScFv BIND	ING TO PURI	SCFV BINDING TO PURIFIED PROTEINS IN ELISA	S IN ELISA
SMIP NAME	ScFv CLONE NAME	CHO-ECD	CHO-CR2	SKBR3	ECD	EQR	Her018	L1-CR1
	S1R2A_CS_1D11	++	+	+	1	ı	1	•
	S1R2C_CS_1D3	+++++++++++++++++++++++++++++++++++++++	‡	‡	-/+	-/+	•	•
	S1R2A_CS_1D3_1	+	‡	+	I		1	ı
	S1R2A_CS_1F7_1	++	++	+	*"	* 1	*	•
HER030	S1R3B2_BMV_1H5	+ +	‡	+	*	*,	* '	•
	S1R3C1_CS_1D3	+	‡	++	+	+	•	٠
HER032	S1R3B2_DP47_1E10	+++++++++++++++++++++++++++++++++++++++	‡	+	3	ı	•	•
HER033	S1R3C1_CS_1B10	+++++	‡	‡	++++	÷	++	1
HER034	S1R3C1_CS_1A6	‡	‡	+	*	* 1	* "	•
HER035	S1R3B2_DP47_1E8	+	+	+	*	*	•	,
	S1R3B2_BMV_1E1	‡	+	+	•		•	•
	S1R3B2_BMV_1G2	+	+	+	+	+	+	
	S1R3B2_DP47_1C9	+	+	+	*	*	•	
HER039	S1R2C_CS_1H12	++	++	++	•		•	•
					ECD	EQR	Her018	L1-CR1
HER071	S1R3A1_BMV_1F3				+++++++++++++++++++++++++++++++++++++++	++++	+++++++++++++++++++++++++++++++++++++++	•
HER072	S1R3A1_BMV_1G4				•	•	•	1
HER073	S1R3A1_CS_1B9				+	+	÷	+
HER074	S1R3A1_CS_1B10				-/+	+	+	+
HER075	S1R3A1_CS_1B12				-/+	+	1	•
HER076	S1R3A1_CS_1D11				•		•	1
	S1R3A1_DP47_1A6				+	+	+	I
HER078	S1R3B1_BMV_1A1				+	+	1	ı
	S1R3B1_BMV_1A10				•		•	·
HER080	S1R3B1_BMV_1C12				-/+		•	P
HER081	BM				-/+		•	
	BA				-/+	·	•	·
	S1R3B1_BMV_1H9				-/+		•	ı
	S1R3B1_BMV_1H11				++	‡	‡	‡
HER085	S1R3B1_DP47_1E1				+		•	•
	S1R3C1_BMV_1H11				•	•	•	•
HER087	S1R3C1_DP47_1H1				1		-	-
			Ľ	Figure 5				



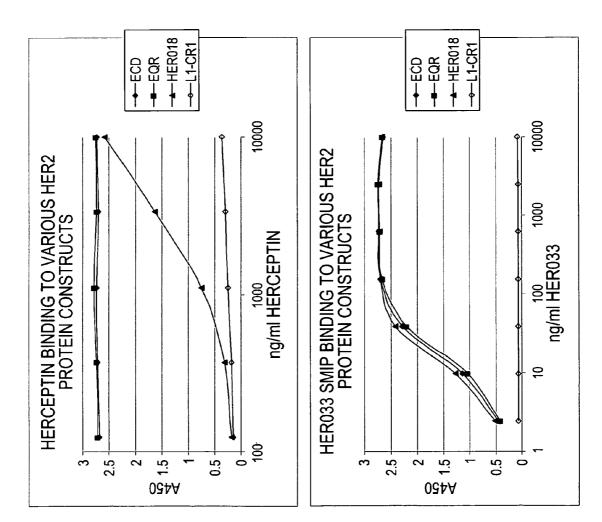
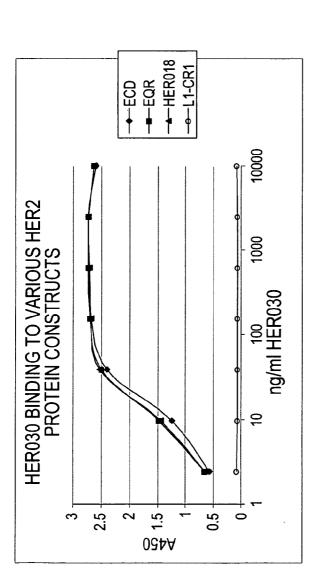


Figure 7



BIACORE DATA FOR HERCEPTIN/HER018 (HERCEPTIN SMIP)/HER067 (AKA HER033) BINDING TO ECD/HER018/HER020

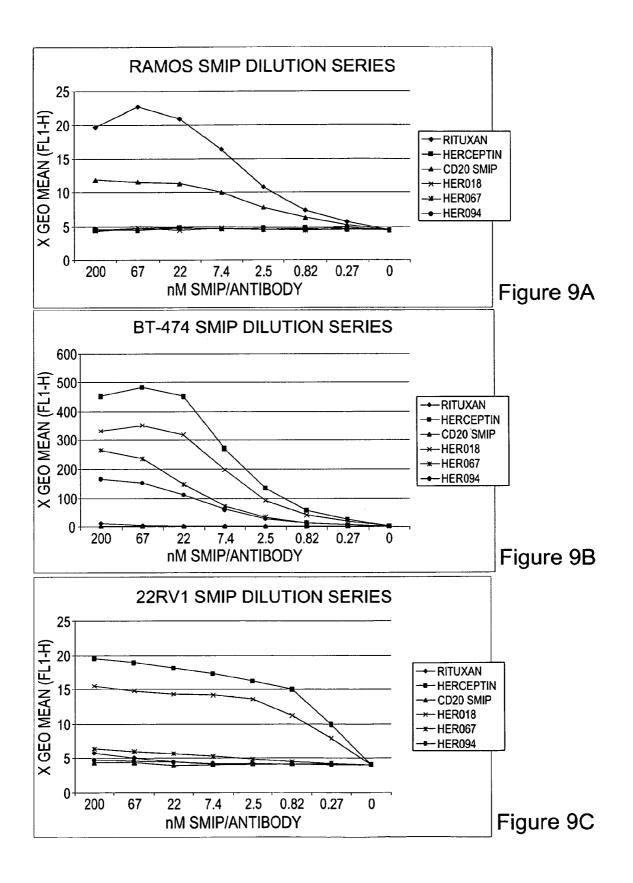
		K _D (M)	
	ECD	HER018	HER020
HERCEPTIN	1.06E-09	2.28E-07	NB*
HERCEPTIN SMIP (HER018)	1.40E-09	1.67E-07	NB*
HER067 (AKA HER033)	8.18E-09	6.47E-09	NB*
HER030	3.56E-08	2.76E-08	NB*

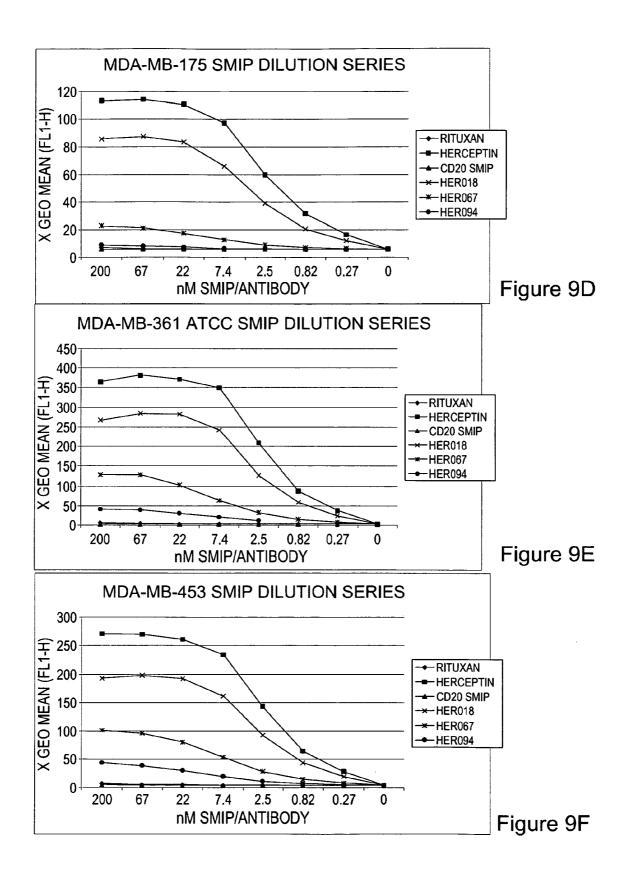
*NB; NO BINDING

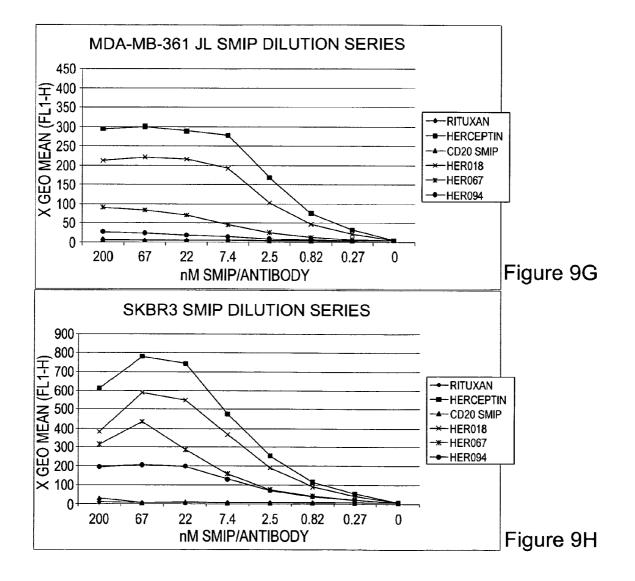
Figure 7 (continued)

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	2 Jurk												-		_																			
	CHO-muHei				+	ı			ı							•	•	+							ı	ı								
	22M1					ı			\$							‡	‡															ı		
	MDA-MB-175 22rv1CHO-muHer2 Jurkat-mcSIIS					-/+			‡							+++	+++																	
Cell Binding	MDA-MB-361 (JL)					‡			‡							+ + +	+++															ı		
ŏ	MDA-MB-361 MDA-MB-361 (ATCC) (JL)					‡	•		* + + +							+++++	+++															ı		
	BT474 MDA-MB-453					‡			‡							+++	+++	++++	‡	+ + +	+		-/+	‡	•								ı	
	BT474					++ ++			+ + +							+++	+++	‡	‡	‡	+		‡	‡	1							•	•	•
	SKBR3	1	+/++	+	+/++	* +/++	÷	9	++/+++	+/++	g	+	+/++	‡	+	+++																		
	mesiis CHOCR2	+/++	+/++	+		* #	‡	QN	+++	+	g	+	+	‡	+	+++																		
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	1.8		1	+	‡	‡	+	•	‡	+	g	+	‡		‡	‡		+	+	+	+	-	+	+	1		1	•	ı	•	'	'	•	<u> </u>
	EQR	+	+	• +	+	‡	+	+	‡	+	Ð	+	+		‡	+ + +		+	+	+	+		+	+	+		•	۱	1	•	1	1	'	'
	SIIS	+	+	• +	‡	‡	+	+	‡	+	+	+	+	‡	‡	‡	+	+	+	+	+		+	+	+		'	ı	•	•	•	+	,	
Trubion	name	HFR026	HER027	HFR028	HFR029	HER030	HER031	HER032	HER033	HER034	HER035	HER036	HER037	HER038	HER039	Herceptin	HER018	HER071	HER072	HER073	HER074	HER075	HER076	HER077	HER078	HER079	HER080	HER081	HER082	HER083	HER084	HER085	HER086	HER087

Figure 8

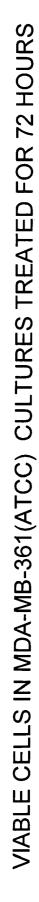


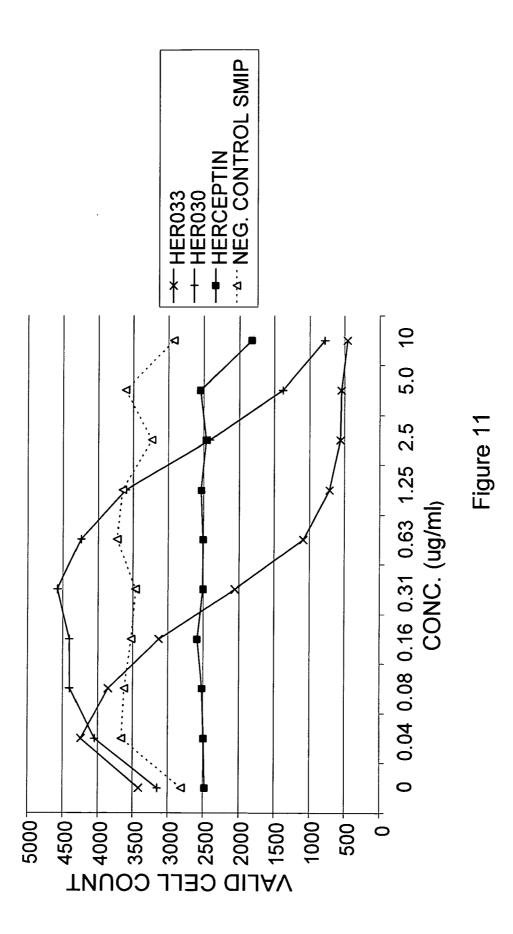




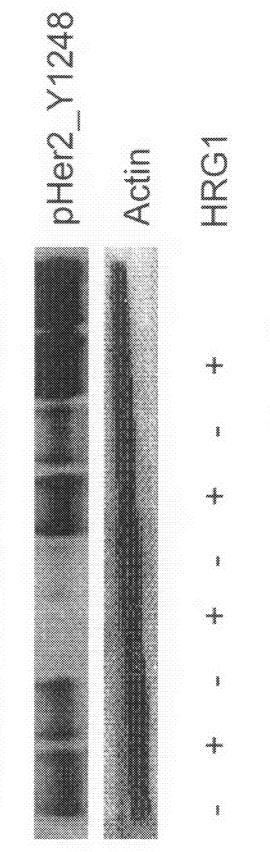
		ANTI-PROLIFERATION ACTIVITY	ION ACTIVITY
		HERCEPTIN	HER033
SKBR3	BREAST	+	+
BT474	BREAST	+	÷
MDA-MB-453	BREAST	0	÷
MDA-MB-361	BREAST	0	Ŧ
JIMT	BREAST	0	0
MCF-7	BREAST	0	0
NCI-N87	GASTRIC	+	0
OVCAR-3	OVARIAN	0	0
SKOV3	OVARIAN	0	TBD

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	SKOV3								0							0			-																
	OVCAR-3 S								0							0																			
	NCI-N87					-	0	0	0				0	0		+																			
rdU)	MDA-MB-175					0	0	0	0				0	0		+	+																		
d/or B	MCF-7								0							0			-																
P an	TMIL								0							0										_									
Negative Proliferation (ATP and/or BrdU)	MDA-MB-361 (JL)								+							0	0																		Figure 12
ative Prolif	MDA-MB-361 (Wyeth)								+		-					0																	-		Fig
Neg:	MDA-MB-361 (ATCC)					+			‡							0	+																		
	MDA-MB-453					+	0	0	+				0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	00	0	
	BT-474	0	0	0	0	+	0	0	+	0	0	0	0	0	0	+	++																		
	SKBR3	0	0	0	0	+	0	0	+	0	0	0	0	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	00	5	
Trubion	name	HER026	HER027	HER028	HER029	HER030	HER031	HER032	HER033	HER034	HER035	HER036	HER037	HER038	HER039	Herceptin	HER018	HER071	HER072	HER073	HER074	HER075	HER076	HER077	HER078	HER079	HER080	HER081	HER082	HER083	HER084	HER085	HER086	HEK087	



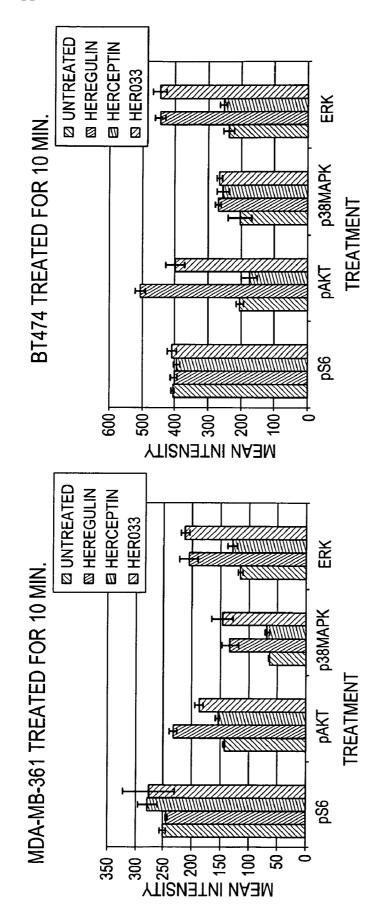
10 ug/ml

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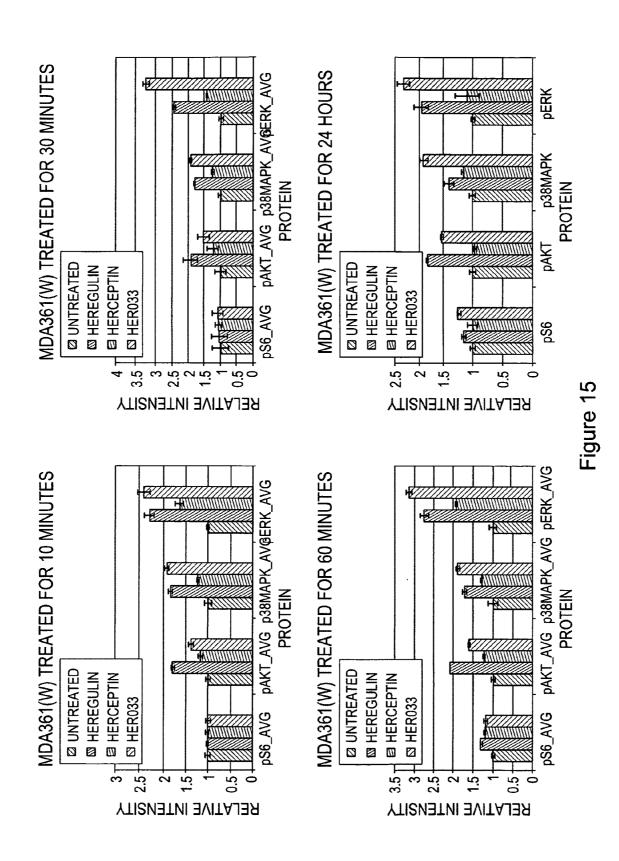
Her033

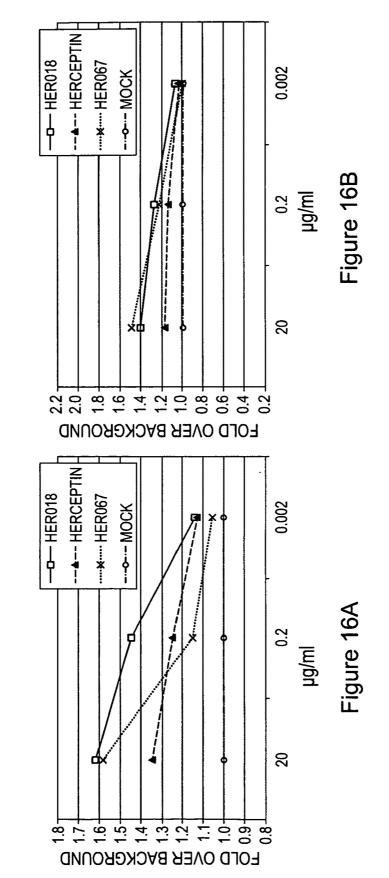
Her2 Kinase Inhibitor

Control











MDA-MB-361 AT 10 MIN. - pErbB2

	Herceptin have different effects on the cell cycle in cell lines where					
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	HER033 and					

HER033 and Herceptin have anti-proliferative effects on SKBR3 and BT474 cells.

SKBK3

	G1 phase	s bas bas	G2M phase
Herceptin	60.38+/- 0.65	15.53+/-0.34	16.70+/-0.32
Heregulin	55 MAY 1 23	47.54+/-0.62	11.13+/-1.46
HERO33	35.65+/-1.86	48.02+/-2.31	10.78+/-1.02
control	53.98+/-2.34	24.71+/-0.86	14.54+/-1.49

**BT474** 

	G1 phase	S phase	G2M phase
Herceptin	72.34+/-0.32	14.50+/-0.72	10.34+/-0.48
Heregulin	68 E-X-1 # 5E	52.67+/-1.48	7.90+/-0.08
HERO33	46.54+/-0.59	43.75+/-0.81	7.52+/-0.25
control	60.80+/-1.80	25.31+/-0.63	11.48+/-2.03

Values that are significantly greater are shown in light gray Values that are significantly lower are shown in darker gray

Figure 17

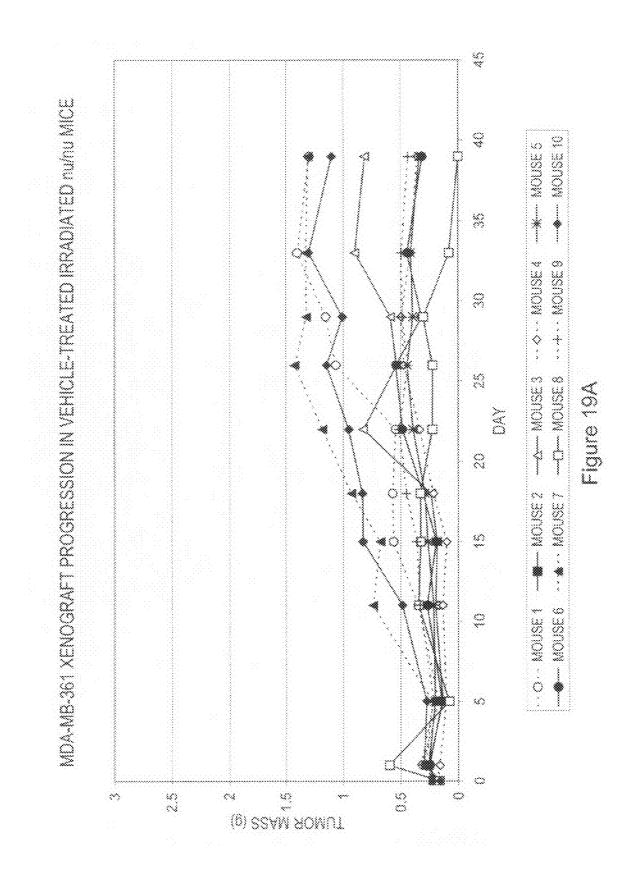
HER033 has anti-proliferative effects on MDA-MB-453 and MDA-MB-361 cells; HER033 has different effects on the cell cycle in Herceptin-resistant cell lines Herceptin has no anti-proliferative effect.

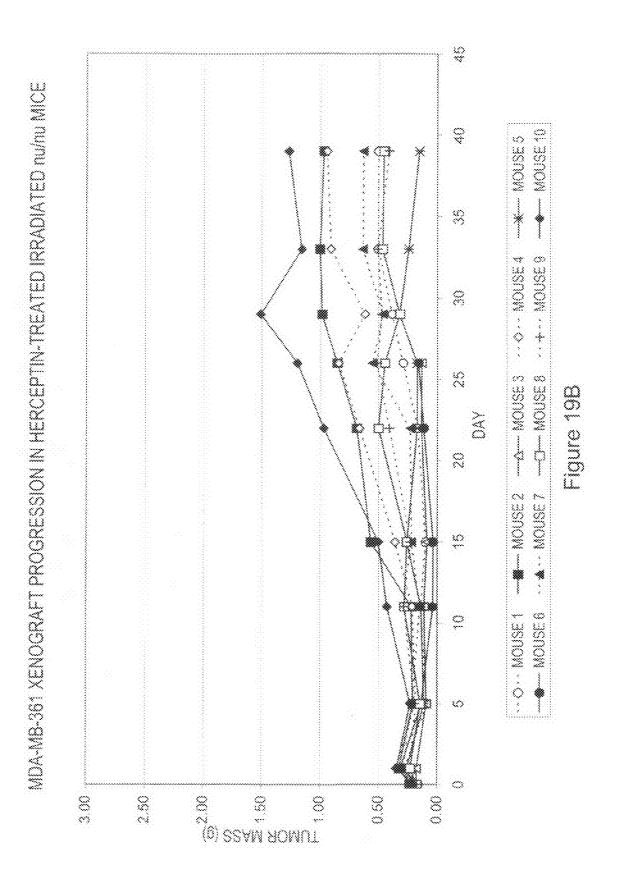
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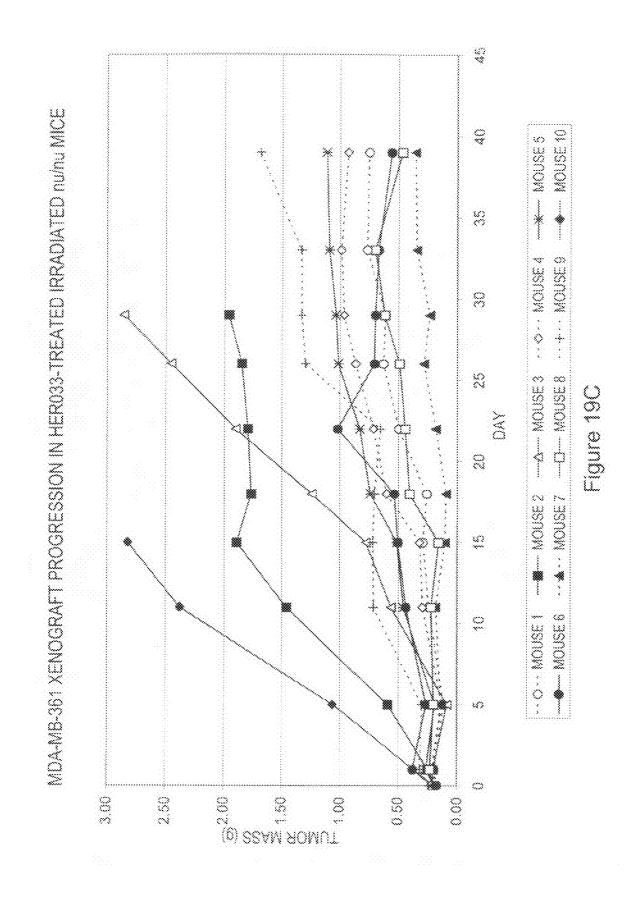
	61 phase	s bhase	GZN phase
Herceptin	55.71+/-1.62	24.56+/-	14.25+/-0.82
Heregulin	46.13+/-0.70	41.32+/- 0.43	10.71+/-0.45
HERO33	68.93+/-1.70	20 89+/	8.48+/-0.41
ontrol	46.38+/-0.92	35,48+/- 0.22	14.87+/-0.93

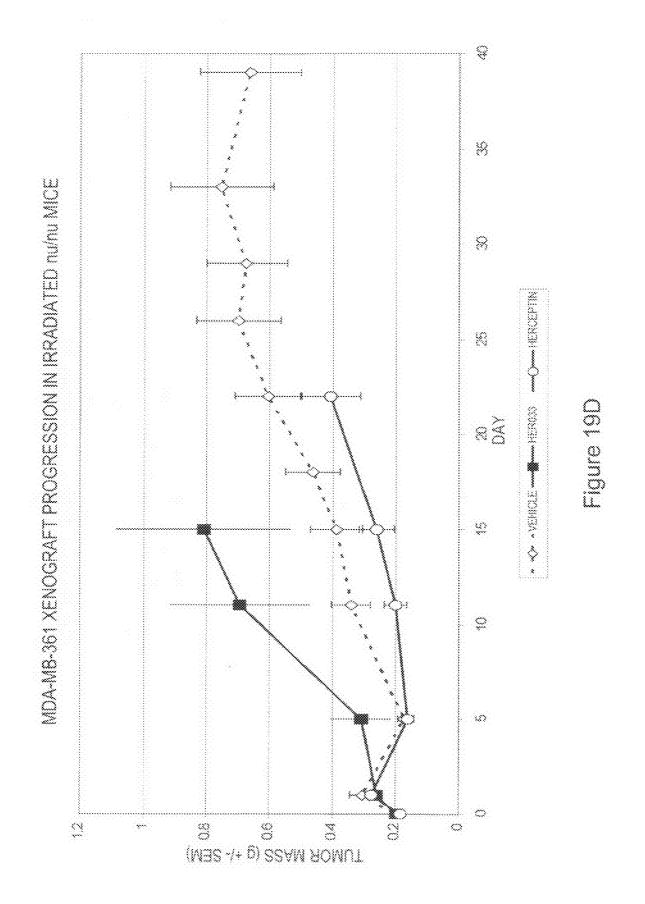
# **MDA-MB-36**

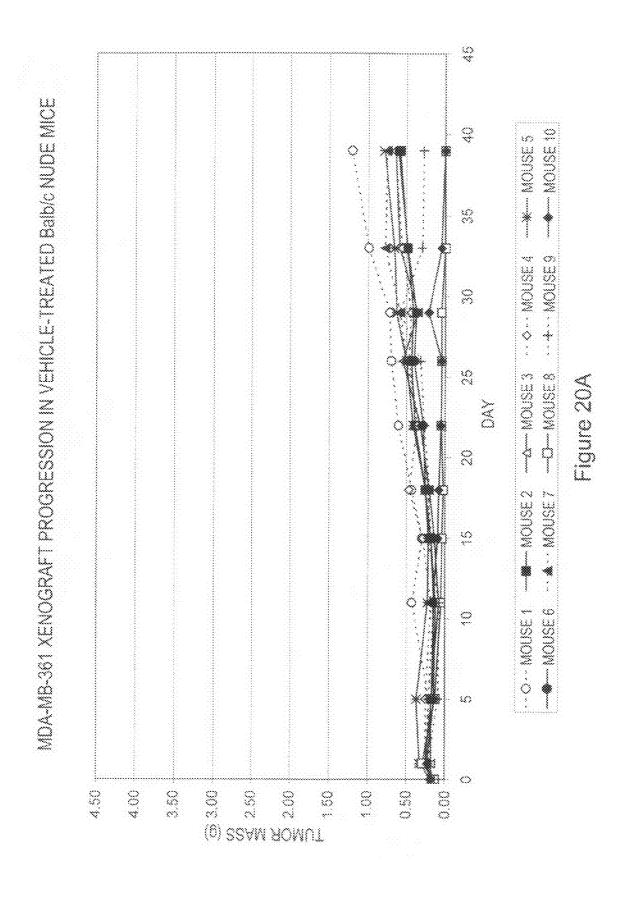
	G1 phase	S phase	GZM Diase
Herceptin	68.62+/-0.74	16.99+/-0.72	9.56+/-1.58
Heregulin	68.03+/-0.49	27.76+/-0.25	6.31+/-0.67
HERO33	78.12+/-0.80	13.19+/-0.87	5.24+/-0.65
control	69.86+/-1.23	14.44+/-0.20	9.51+/-1.09
Values that Values that	Values that are significantly greater are shown in light gray Values that are significantly lower are shown in darker gray	significantly greater are shown in light gra significantly lower are shown in darker gr	m in light gray in darker gray

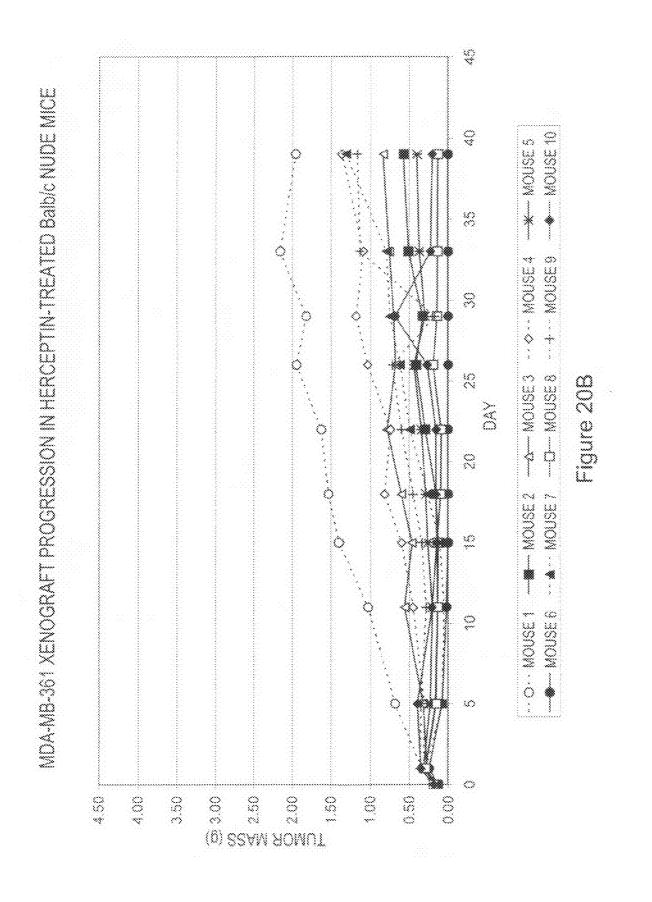


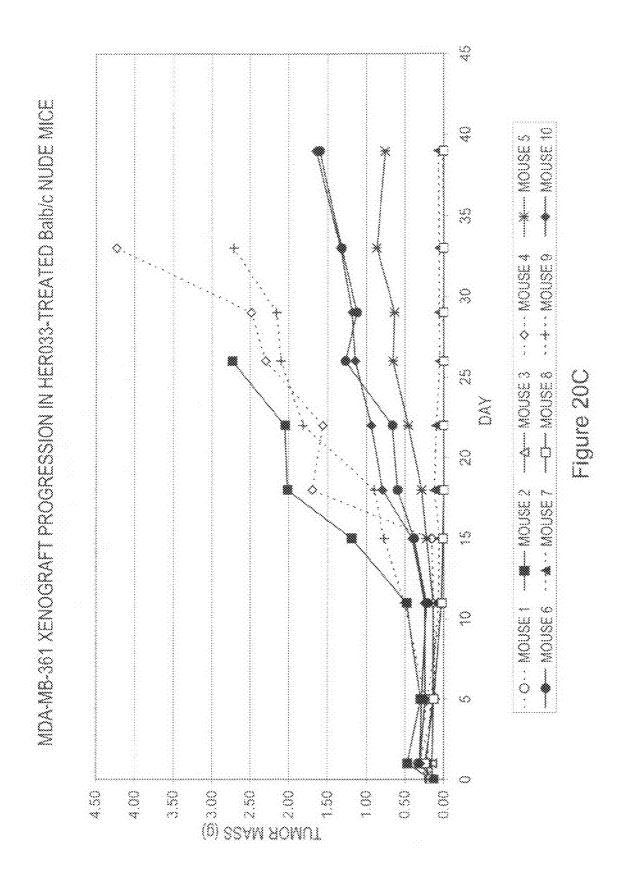




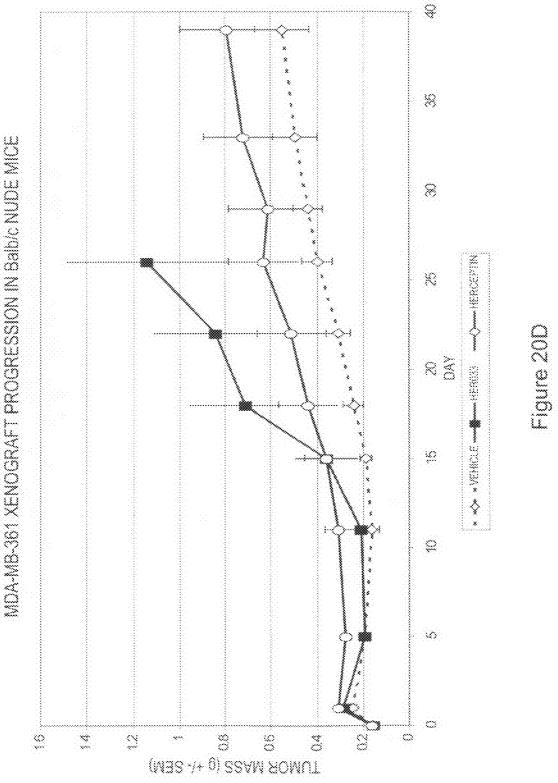




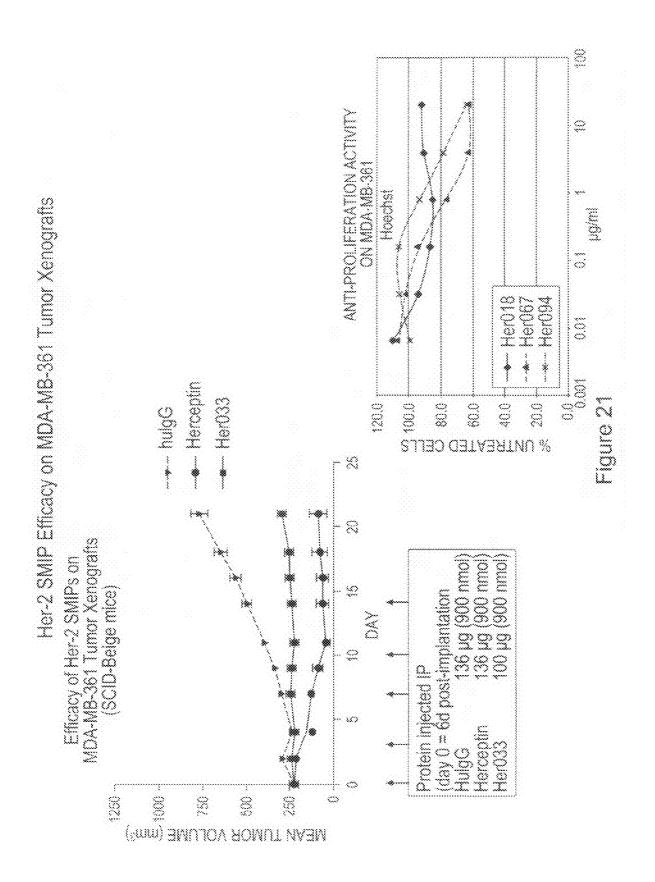








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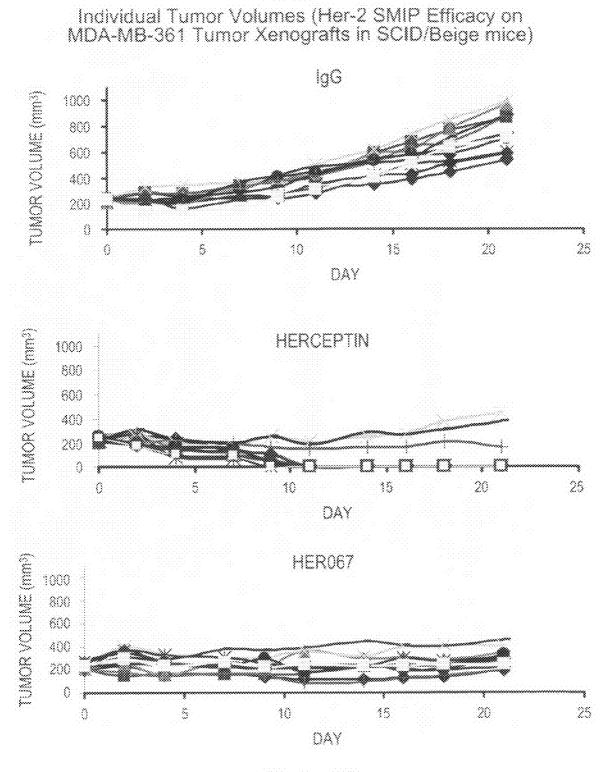


Figure 22

# THERAPEUTIC COMPOSITIONS AND METHODS

# CROSS REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims the benefit of U.S. Provisional Application Ser. No. 60/932,302, filed May 29, 2007.

# FIELD OF THE INVENTION

**[0002]** This invention relates to binding proteins that bind erythroblastic leukemia viral oncogene homolog 2 (ErbB2), in particular, human ErbB2 (also known as HER2), and their use in regulating ErbB2-associated activities. The binding proteins disclosed herein are useful in diagnosing, preventing, and/or treating ErbB2 associated disorders, e.g., hyperproliferative disorders, including cancer, and autoimmune disorders, including arthritis.

#### BACKGROUND OF THE INVENTION

[0003] The ErbB family of receptor tyrosine kinases are important mediators of cell growth, differentiation and survival. The receptor family includes four distinct members including epidermal growth factor receptor (EGFR or ErbB1), HER2 (ErbB2 or p185^{neu}), HER3 (ErbB3) and HER4 (ErbB4 or tyro2). Structurally, the ErbB receptors possess an extracellular domain (with four subdomains, I-IV), a single hydrophobic transmembrane domain, and (except for HER3) a highly conserved tyrosine kinase domain. Crystal structures of EGFR reveal a receptor that adopts one of two conformations. In the "closed" conformation, EGFR is not bound by ligand and the extracellular subdomains II and IV remain tightly apposed, preventing inter-receptor interactions. Ligand binding prompts the receptor to adopt an "open" conformation, in which the EGFR receptor is poised to make inter-receptor interactions.

**[0004]** The ErbB receptors are generally found in various combinations in cells and heterodimerization is thought to increase the diversity of cellular responses to a variety of ErbB ligands. EGFR is bound by at least six different ligands; epidermal growth factor (EGF), transforming growth factor alpha (TGF- $\alpha$ ), amphiregulin, heparin binding epidermal growth factor (HB-EGF), betacellulin and epiregulin. A family of heregulin proteins resulting from alternative splicing of a single gene are ligands for ErbB3 and ErbB4. The heregulin family includes alpha, beta and gamma heregulins, neu differentiation factors (NDFs), glial growth factors (GGFs); ace-tylcholine receptor inducing activity (ARIA); and sensory and motor neuron derived factor (SMDF).

**[0005]** HER2 was originally identified as the product of the transforming gene from neuroblastomas of chemically treated rats. The activated form of the neu proto-oncogene results from a point mutation (valine to glutamic acid) in the transmembrane region of the encoded protein. Amplification of the human homolog of neu is observed in breast and ovarian cancers and correlates with a poor prognosis. Overexpression of ErbB2 (frequently but not uniformly due to gene amplification) has also been observed in other carcinomas including carcinomas of the stomach, endometrium, salivary gland, lung, kidney, colon, thyroid, pancreas and bladder.

**[0006]** HER2 has been suggested to be a ligand orphan receptor. Ligand-dependent heterodimerization between HER2 and another HER family member, HER1, HER3 or HER4, activates the HER2 signaling pathway. The intracel-

lular signaling pathway of HER2 is thought to involve ras-MAPK and PI3K pathways, as well as MAPK-independent S6 kinase and phospholipase C-gamma signaling pathways. HER2 signaling also effects proangiogenic factors, vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8), and an antiangiogenic factor, thrombospondin-1 (TSP-1).

**[0007]** The full-length ErbB2 receptor undergoes proteolytic cleavage releasing its extracellular domain (ECD), which can be detected in cell culture medium and in patient's sera. The truncated ErbB2 receptor (p95ErbB2) that remains after proteolytic cleavage exhibits increased autokinase activity and transforming efficiency compared with the full-length receptor, implicating the ErbB2 ECD as a negative regulator of ErbB2 kinase and oncogenic activity.

[0008] A recombinant humanized version of the murine anti-ErbB2 antibody 4D5 (huMAb4D5-8, rhuMAb HER2 or HERCEPTIN®; U.S. Pat. No. 5,821,337) is clinically active in patients with ErbB2-overexpressing metastatic breast cancers that have received extensive prior anti-cancer therapy (Baselga et al., J. Clin. Oncol. 14:737-744 (1996)). HERCEP-TIN® reportedly targets the C-terminal region of domain IV of ErbB2. HERCEPTIN® clinical activity is predominately dependent on antibody dependent cell mediated cytotoxicity (ADCC). Studies have suggested that HERCEPTIN® acts by triggering G1 cell cycle arrest. Presently ErbB-directed therapeutics do not meet the current medical needs. ErbB-directed therapeutics have had only modest anti-tumor efficacy and are not as potent as anticipated from preclinical models. In most patients who initially respond to HERCEPTIN®, disease progression is noted within 1 year. In the metastatic setting, a median duration of roughly nine months was reported, at which point it appears that patients frequently become refractory to therapy. Studies have suggested that more complete blockade of the ErbB receptor family would be beneficial. As there are multiple functional domains of HER2, agents targeted to each of the domains could be a potentially valuable therapeutic. Additionally, there are harmful side effects of HERCEPTIN® treatment. Cardiac dysfunction, quantitated as a decrease in left ventricular ejection fraction (LVEF) of 10% from baseline or less than 50% total, was identified in roughly 7.1% of patients receiving HERCEPTIN® for 1 year versus 2.2% in patients randomized to observation in the HERA trial. Rates of severe and symptomatic congestive heart failure (CHF) were also significantly higher in the group randomized to HERCEPTIN®. Potentially, agents targeting a different HER2 epitopes could avoid these side effects. Accordingly, there remains an urgent need for agents targeting HER2.

**[0009]** The EGFR family of receptor tyrosine kinases are important regulators of cell growth and proliferation. One member of the family, ErbB2, has been implicated in a host of disorders and diseases including many forms of cancer.

**[0010]** Accordingly, there is an urgent need for therapeutic and diagnostic agents for detecting and treating ErbB2-mediated disorders including proliferative disorders.

## SUMMARY OF THE INVENTION

**[0011]** The invention relates to novel ErbB2 binding proteins that bind the extracellular domain (ECD) of ErbB2, in particular, human ErbB2. The novel binding protein can be antibody, an antigen-binding fragment of an antibody or a small modular immunopharmaceutical (SMIP). In various embodiments, the binding proteins: bind the ECD in the L1, CR1, L2 or CR2 domain, are ErbB2 agonists, increase tyrosine phosphorylation of ErbB2 and/or of AKT, MAP kinase (MAPK) or ERK 1/2, preferentially bind ErbB2 ECD homodimer over monomer or shed ECD, reduces ErbB2 mediated proliferation of cancer cells, increase apoptosis in cancer cells, increase the number of cells in S phase after treatment with the binding protein and reduce tumor growth in vivo, or any combination of these properties.

**[0012]** The invention further relates to nucleic acids encoding the binding proteins or their components, vectors and host cells comprising the nucleic acids and methods of producing the binding proteins by expressing them in the host cells.

**[0013]** In a further aspect, the invention provides kits and compositions comprising one or more binding proteins of the invention and in some embodiments, further comprising an additional component that is a therapeutic or diagnostic agent, particularly a chemotherapeutic agent.

**[0014]** The invention also provides methods for producing and identifying binding proteins of the invention and methods for using them, including for treating cancer or other ErbB2 mediated disorders in a subject in need thereof, for reducing proliferation of and/or increasing apoptosis in ErbB2 expressing cells, including cancer cells, for reducing tumor growth and for diagnostic uses, including detecting and/or quantifying the presence of ErbB2 or cells expressing it.

## BRIEF DESCRIPTION OF THE FIGURES

**[0015]** FIG. 1. Schematic representation of the selection strategy used in the generation of human anti-Her2 scFv binding domains.

[0016] FIG. 2 (A-M). Alignments of the heavy chain amino acid sequences of human anti-Her2 scFvs with the germline human  $V_H$  gene sequence. CDRs are in bold type.

[0017] FIG. 3 (A-L). Alignments of the light chain amino acid sequences of human anti-Her2 scFvs with the germline human  $V_{\kappa}$  or  $V_{\lambda}$  sequence. CDRs are in bold type.

**[0018]** FIG. **4**. (A) Schematic diagram of the protein constructs used for selection and screening of scFvs and SMIPs that bind to the extracellular domain of Her2. (B) scFvs and SMIPs are binned into 4 distinct groups according to their binding phenotype as determined using the reagents in FIG. **4**A. (* Herceptin contact sites)

[0019] FIG. 5. ELISA data for scFv binding to Her2. Binding data for phage-expressed scFv binding to Her2-expressing cells is shown on the left side of the table and data for soluble scFv binding to purified Her2 proteins is shown on the right. ELISA data is scored using a range that correlates with binding signal as indicated by -, + etc.

**[0020]** FIG. 6. Binding of HER2 SMIPs (HER067 and HER030), HERCEPTIN® (trastuzumab), and a trastuzumab SMIP (HER018) to (A) HER2 dimer; (B) HER2 monomer; and (C) HER2 shed ectodomain found in SKBR3 supernatant.

**[0021]** FIG. 7. ELISA and BIACORE® data for HERCEP-TIN® (trastuzumab) and SMIPs binding to Her2. Graphs represent binding of HERCEPTIN® (trastuzumab), Her033 or Her030 binding to various Her2 proteins determined by standard ELISA methods. The table represents Kd values for HERCEPTIN® (trastuzumab), Her033, Her030 and Her018 (Herceptin SMIP) binding to various Her2 proteins as detected by BIACORE®.

**[0022]** FIG. **8** provides a summary of various specific SMIPs, HERCEPTIN® (trastuzumab), and a trastuzumab SMIP (HER018) binding to various HER2 molecules (differ-

ent sizes and different species, including human, murine, and macaque) as well as binding to several different cancer cell lines.

[0023] FIGS. 9A-9H show cell surface binding of HER2 SMIPs (HER067 and HER094), HERCEPTIN® (trastuzumab), and a trastuzumab SMIP (HER018) to cell lines (A) Ramos (Her2⁻/CD20⁺ control); (B) BT474; (C) 22rv1; (D) MDA-MB-175; (E) MDA-MB-361 (ATCC); (F) MDA-MB-453; (G) MDA-MB-361 (JL); and (H) SKBR3.

**[0024]** FIG. **10** provides a summary of the anti-proliferative activity of HER033 SMIP and HERCEPTIN® (trastuzumab) on several different cancer cell lines.

**[0025]** FIG. **11**. Proliferation of MDA-MB-361 cells following treatment with HER030 or HER033. MDA-MB-361 (ATCC) breast cancer cells were plated in 96-well format and treated with 0-10 ug/ml anti-Her2 or control reagents for 72 hr. Cells were washed, fixed, and stained with DAPI. Stained nuclei were counted using Cellomics High Content assay measuring fluorescence at 360 nM.

**[0026]** FIG. **12** provides a summary of the anti-proliferative activity of various specific SMIPs, HERCEPTIN® (trastuzumab), and a trastuzumab SMIP (HER018) on several different cancer cell lines.

[0027] FIG. 13. Western blot analysis of effect of Her033 on Her2 receptor phosphorylation (Y1248) following 24 hr treatment of MDA-MB-361 breast cancer cells. Cells were treated in vitro with Her033, HERCEPTIN® (trastuzumab), or a small molecule Her2 kinase inhibitor for 24 hrs either alone or in the presence of heregulin (HRG1 10 ng/ml) activation of Her3. Protein lysates (50 ug/well) were size fractionated by SDS-PAGE, transferred to nitrocellulose and probed with anti-phospho-Her2(Y1248) antibody. Inhibition of the Her2 receptor kinase blocked the endogenous Her2 autophosphorylation at tyrosine 1248 relative to control. Treatment with Herceptin did not significantly modulate receptor phosphorylation whereas treatment with Her033 stimulated Her2 receptor phosphorylation. Western blots were subsequently reprobed with anti-Actin antibody as protein loading control.

**[0028]** FIG. **14**. Her033 increases downstream phosphoprotein signal transduction in MDA-MB-361 and BT474 breast cancer cells. Cells were plated in 96-well format and treated with anti-Her2 reagents or Heregulin for 10 minutes. Cells were stained with either rabbit anti-pAKT, anti-pERK, anti-pS6K, or anti-p38MAPK antibodies and ALEXA594 labeled secondary antibody and cellular fluorescence quantified by high content (Cellomics) analysis. In both breast cancer cell lines, treatment with Her033 SMIP induces phosphorylation of AKT and ERK proteins similar to treatment with the Her3 ligand Heregulin. MDA-MB-361 cells also demonstrate significant activation of p38MAP kinase.

**[0029]** FIG. **15**. Kinetic analysis of Her033 stimulated downstream effector phosphorylation in MDA-MB-361 breast cancer cells. Cells were grown in 96-well format and treated with either anti-Her2 reagents or Her3 ligand Heregulin for 10 min to 24 hr as indicated. Cells were stained with either rabbit anti-pAKT, anti-pERK, anti-pS6K, or anti-p38MAPK antibodies and ALEXA594 labeled secondary antibody and cellular fluorescence quantified by high content (Cellomics) analysis. Her033 treatment induces sustained activation of AKT, ERK and p38MAP kinase phosphorylation in this cell line similar in magnitude to levels following stimulation with 10 ng/ml Heregulin.

**[0030]** FIGS. **16**A and **16**B show level of phosphorylation of ErbB2, and ERK1/2 in MDA-MB-361 cells when treated with HER2 SMIP HER067, HERCEPTIN® (trastuzumab), and a trastuzumab SMIP (HER018).

**[0031]** FIG. **17** shows the effect on cell cycle of HER033 SMIP, HERCEPTIN® (trastuzumab), and heregulin on the SKBR3 and BT474 cell lines.

**[0032]** FIG. **18** shows the effect on cell cycle of HER033 SMIP, HERCEPTIN® (trastuzumab), and heregulin on the MDA-MB-453 and MDA-MB-361 cell lines.

[0033] FIG. 19. MDA-MB-361 xenograft progression in irradiated nu/nu mice. Female nu/nu mice were exposed to 400 rads of total body irradiation. After three days, they were injected subcutaneously in the dorsal right flank with  $1 \times 10^7$  MDA-MB-361 cells in Matrigel. When the tumors had reached a mass of 0.1-0.25 g, animals were dosed with Herceptin, HER033, or vehicle (100 ug/mouse, intraperitoneally) on days 1, 4, 6, 8 and 11 (n=10 mice/treatment group). Tumors were measured, and calculated tumor volumes for individual mice are shown for animals treated with vehicle (A), Herceptin (B), or HER033 (C). Animals developing tumors larger than 2.5 g were sacrificed. The mean tumor volume±SEM are plotted in (D). Means were not calculated for treatment groups in which animals with large tumors had been sacrificed.

**[0034]** FIG. **20**. MDA-MB-361 xenograft progression in Balb/c nude mice. Male Balb/c nude mice were injected subcutaneously in the dorsal right flank with  $1 \times 10^7$  MDA-MB-361 cells in Matrigel. When the tumors had reached a mass of 0.1-0.25 g, animals were dosed with HERCEPTIN® (trastuzumab), HER033, or vehicle (100 ug/mouse, intraperitoneally) on days 1, 4, 6, 8 and 11 (n=10 mice/treatment group). Tumors were measured, and calculated tumor volumes for individual mice are shown for animals treated with vehicle (A), HERCEPTIN® (trastuzumab) (B), or HER033 (C). Animals developing tumors larger than 2.5 g were sacrificed. The mean tumor volume±SEM are plotted in (D). Means were not calculated for treatment groups in which animals with large tumors had been sacrificed.

[0035] FIGS. 21 and 22 show the in vivo efficacy of HER2 SMIP HER033/HER067 when used to treat SCID-Beige having a tumor xenograft of MDA-MB-361 cells and the in vitro anti-proliferative activity on MDA-MB-361 cells. The top panel of FIG. 21 shows the mean tumor volume in mice treated with HER033 SMIP, HERCEPTIN® (trastuzumab), or vehicle (IgG) after 21 days. The bottom panel of FIG. 21 shows a titration of anti-proliferative activity of HER2 SMIPs (HER067 and HER094) and trastuzumab SMIP (HER018) on the MDA-MB-361 cells used for xenografting in the mice. FIG. 22 shows the tumor volume of individual mice in each treatment group.

#### DETAILED DESCRIPTION OF THE INVENTION

## I. Definitions

**[0036]** In order that the present invention may be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description. The present invention provides novel binding proteins that, specifically bind the extra cellular domain (ECD) of ErbB2, especially human ErbB2. In some embodiments, the binding protein is an antibody or an antigen binding fragment of such

antibody that specifically binds the ECD. In other embodiments, the binding protein is a small modular immunopharmaceutical (SMIP).

**[0037]** The term "antibody" refers to an intact four-chain molecule having 2 heavy chains and 2 light chains, each heavy chain and light chain having a variable domain and a constant domain, or an antigen-binding fragment thereof, and encompasses any antigen-binding domain. In various embodiments, an antibody of the invention may be polyclonal, monoclonal, monospecific, polyspecific, bi-specific, humanized, human, chimeric, synthetic, recombinant, hybrid, mutated, grafted (including CDR grafted), or an in vitro generated antibody.

[0038] The term "antigen-binding fragment" of an antibody that specifically binds the ECD of ErbB2 refers to a portion or portions of the antibody that specifically binds to the ECD. An antigen-binding fragment may comprise all or a portion of an antibody light chain variable region  $(V_L)$  and/or all or a portion of an antibody heavy chain variable region  $(V_H)$  so long as the portion or portions are antigen-binding. However, it does not have to comprise both. Fd fragments, for example, have two  $V_H$  regions and often retain some antigenbinding function of the intact antigen-binding domain. Examples of antigen-binding fragments of an antibody include (1) a Fab fragment, a monovalent fragment having the  $V_L, V_H, C_L$  and  $C_H 1$  domains; (2) a F(ab')₂ fragment, a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; (3) a Fd fragment having the two  $V_H$  and  $C_H$  1 domains; (4) a Fv fragment having the  $V_L$  and  $V_H$ domains of a single arm of an antibody, (5) a dAb fragment (Ward et al., (1989) Nature 341:544-546), that has a  $V_{\mu}$ domain; (6) an isolated complementarity determining region (CDR), and (7) a single chain Fv (scFv). Although the two domains of the Fv fragment,  $V_L$  and  $V_H$ , are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the  $V_L$  and  $V_H$  regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are evaluated for function in the same manner as are intact antibodies.

**[0039]** The term "effective amount" refers to a dosage or amount that is sufficient to alter ErbB2 activity, to ameliorate clinical symptoms or achieve a desired biological outcome, e.g., decreased cell growth or proliferation, decreased heterodimerization with another member of the EGF family decreased homodimerization, decrease tumor growth rate or tumor size, increased cell death etc.

**[0040]** The term "human antibody" includes antibodies having variable and constant region sequences corresponding substantially to human germline immunoglobulin sequences known in the art, including, for example, those described by Kabat et al. (See Kabat, et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). The amino acid sequences of a human antibody, when aligned with germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific

mutagenesis in vitro or by somatic mutation in vivo). Such non-germline residues may occur in a framework region, a CDR, for example in the CDR3, or in the constant region. A human antibody can have one or more residues, such as any number from 1-15, including all of the integers between 1 and 15, or more, replaced with an amino acid residue that is not encoded by the human germline immunoglobulin sequence. CDRs are as defined by Kabat or in Chothia C, Lesk A M, Canonical structures for the hypervariable regions of immunoglobulins, J Mol Biol. 1987 Aug. 20; 196(4):901-17.

[0041] The phrase "inhibit" or "antagonize" an ErbB2/ HER2 activity refers to a reduction, inhibition, or otherwise diminution of at least one activity of ErbB2 due to binding an anti-ErbB2 antibody or antigen binding portion, wherein the reduction is relative to the activity of ErbB2 in the absence of the same antibody or antigen-binding portion. The activity can be measured using any technique known in the art, including, for example, as described in the Examples. Activation of the Her2 receptor tyrosine kinase can be measured by the degree of phosphorylation of key tyrosine residues in the intracellular domain. For example, Tyr1248 is a known site of autophosphorylation and thus is a direct measure of Her2 receptor kinase activity. Typically the degree of phosphorylation can be determined by Western blot analysis probing with anti-phopho-Her2 specific antibodies (eg. Tyr1248, Tyr1139, Tyr1112, Tyr877, Tyr1221/1222). Alternatively, cells can be permeabilized and probed with fluorescently labeled phospho-Her2 antibodies and measured either by flow cytometry or high content (Cellomics) analysis. Additionally, the Her2 receptor can be immunoprecipitated, digested with trypsin protease and the degree of phosphorylation at specific sites within the individual Her2 peptides determined by standard Mass Spec techniques. Inhibition or antagonism does not necessarily indicate a total elimination of the ErbB2 polypeptide biological activity. In some embodiments, the reduction in activity may be about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95% or more, including 100% reduction, i.e., elimination of the activity.

**[0042]** The term "ErbB2" refers to erythroblastic leukemia viral oncogene homolog 2. In the case of human ErbB2, it also is known as c-erb-B2 or HER2/neu. In some embodiments the ErbB2 may comprise: (1) an amino acid sequence of a naturally occurring mammalian ErbB2 polypeptide (full length or mature form) or a fragment thereof, or a fragment thereof; (2) an amino acid sequence substantially identical to, e.g., at least 85%, 90%, 95%, 96%, 97%, 98%, 99% identical to said amino acid sequence or a fragment thereof; (3) an amino acid sequence that is encoded by a naturally occurring mammalian ErbB2 nucleotide sequence or a fragment thereof, or (4) a nucleotide sequence that hybridizes to the foregoing nucleotide sequence under stringent conditions, e.g., highly stringent conditions.

**[0043]** HER2 or c-erb-B2 encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor1. HER2 protein overexpression is observed in 25%-30% of primary breast cancers and is associated with decreased overall survival and a lowered response to chemotherapy and hormonal therapy, which can continue throughout the course of the disease and drives aggressive tumor growth.

**[0044]** The term "ErbB2 activity" refers to at least one cellular process initiated or interrupted as a result of ErbB2 binding to a receptor complex comprising ErbB2 and an ErbB

receptor family member including ErbB1 (EGFR), ErbB2, ErbB3, ErbB4 or comprising an ErbB ligand such as but not limited to EGF, TGF-alpha, amphiregulin, betacellulin, heparin-binding EGF-like growth factor, GP30 on the cell. ErbB2 activity can be determined using any suitable assay methods, for example, protein overexpression can be determined using immunohistochemistry (IHC) and may also be inferred when HER2 gene amplification is identified using fluorescence in situ hybridization (FISH).

**[0045]** As used herein, "in vitro generated antibody" refers to an antibody where all or part of the variable region (e.g., at least one CDR) is generated in a non-immune cell selection (e.g., an in vitro phage display, protein chip or any other method in which candidate sequences can be tested for their ability to bind to an antigen). This term excludes sequences generated by genomic rearrangement in an immune cell.

**[0046]** The term "isolated" refers to a molecule that is substantially free of its natural environment. For instance, an isolated protein is substantially free of cellular material or other proteins from the cell or tissue source from which it was derived. The term also refers to preparations where the isolated protein is sufficiently pure for pharmaceutical compositions; or at least 70-80% (w/w) pure; or at least 80-90% (w/w) pure; or at least 90-95% pure; or at least 95%, 96%, 97%, 98%, 99%, or 100% (w/w) pure.

[0047] The phrase "percent identical" or "percent identity" refers to the similarity between at least two different sequences. This percent identity can be determined by standard alignment algorithms, for example, the Basic Local Alignment Tool (BLAST) described by Altshul et al. ((1990) J. Mol. Biol., 215: 403-410); the algorithm of Needleman et al. ((1970) J. Mol. Biol., 48: 444-453); or the algorithm of Meyers et al. ((1988) Comput. Appl. Biosci., 4: 11-17). A set of parameters may be the Blosum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5. The percent identity between two amino acid or nucleotide sequences can also be determined using the algorithm of E. Meyers and W. Miller ((1989) CABIOS, 4:11-17) that has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity is usually calculated by comparing sequences of similar length.

**[0048]** The terms "specific binding" or "specifically binds" refer to forming a complex that is relatively stable under physiologic conditions. Specific binding is characterized by a high affinity and a low to moderate capacity as distinguished from nonspecific binding which usually has a low affinity with a moderate to high capacity. Typically, binding is considered specific when the association constant  $K_A$  is higher than  $10^6 \text{ M}^{-1}$ . The appropriate binding conditions, such as concentration of antibodies, ionic strength of the solution, temperature, time allowed for binding, concentration of a blocking agent (e.g., serum albumin, milk casein), etc., may be optimized by a skilled artisan using routine techniques. An antibody is said to specifically bind an antigen when the  $K_D$  is  $\leq 1 \text{ mM}$ , preferably  $\leq 100 \text{ nM}$ .

**[0049]** As used herein, the term "stringent" describes conditions for hybridization and washing. Stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Aqueous and nonaqueous methods are described in that reference and either can be used. One example of stringent hybridization conditions is hybridization

tion in  $6\times$  sodium chloride/sodium citrate (SSC) at about  $45^{\circ}$  C., followed by at least one wash in 0.2×SSC, 0.1% SDS at  $50^{\circ}$  C. A second example of stringent hybridization conditions is hybridization in  $6\times$ SSC at about  $45^{\circ}$  C., followed by at least one wash in 0.2×SSC, 0.1% SDS at  $55^{\circ}$  C. Another example of stringent hybridization conditions is hybridization in  $6\times$ SSC at about  $45^{\circ}$  C., followed by at least one wash in 0.2×SSC, 0.1% SDS at  $55^{\circ}$  C. Another example of stringent hybridization conditions is hybridization in  $6\times$ SSC at about  $45^{\circ}$  C., followed by at least one wash in 0.2×SSC, 0.1% SDS at  $60^{\circ}$  C. A further example of stringent hybridization conditions is hybridization in  $6\times$ SSC at about  $45^{\circ}$  C., followed by at least one wash in 0.2×SSC, 0.1% SDS at  $65^{\circ}$  C. High stringent conditions include hybridization in 0.5M sodium phosphate, 7% SDS at  $65^{\circ}$  C., followed by at least one wash at 0.2×SSC, 1% SDS at  $65^{\circ}$  C.

**[0050]** The phrase "substantially as set out," "substantially identical" or "substantially homologous" means that the relevant amino acid or nucleotide sequence (e.g., CDR(s),  $V_{H^3}$  or  $V_L$  domain) will be identical to or have insubstantial differences (through conserved amino acid substitutions) in comparison to the sequences that are set out. Insubstantial differences include minor amino acid changes, such as 1 or 2 substitutions in a 5 amino acid sequence of a specified region. In the case of antibodies, the second antibody has the same specificity and has at least 50% of the affinity of the first antibody.

**[0051]** Sequences substantially identical or homologous (e.g., at least about 85% sequence identity) to the sequences disclosed herein are also part of this application. In some embodiment, the sequence identity can be about 85%, 90%, 95%, 96%, 97%, 98%, 99% or higher. Alternatively, substantial identity or homology exists when the nucleic acid segments will hybridize under selective hybridization conditions (e.g., highly stringent hybridization conditions), to the complement of the strand. The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form.

**[0052]** The term "therapeutic agent" is a substance that treats or assists in treating a medical disorder. Therapeutic agents may include, but are not limited to, anti-proliferative agents, anti-cancer agents including chemotherapeutics, anti-virals, anti-infectives, immune modulators, and the like that modulate immune cells or immune responses in a manner that complements the ErbB2 activity of an anti-ErbB2 binding protein of the invention. Non-limiting examples and uses of therapeutic agents are described herein.

**[0053]** As used herein, a "therapeutically effective amount" of an anti-ErbB2 binding protein refers to an amount of an binding protein that is effective, upon single or multiple dose administration to a subject (such as a human patient) at treating, preventing, curing, delaying, reducing the severity of, and/or ameliorating at least one symptom of a disorder or recurring disorder, or prolonging the survival of the subject beyond that expected in the absence of such treatment.

**[0054]** The term "treatment" refers to a therapeutic or preventative measure. The treatment may be administered to a subject having a medical disorder or who ultimately may acquire the disorder, in order to prevent, cure, delay, reduce the severity of, and/or ameliorate one or more symptoms of a disorder or recurring disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

# II. Anti-ErbB2 Binding Proteins

**[0055]** In a first aspect, the invention provides novel ErbB2/ HER2, particularly human ErbB2/HER2, ErbB2/HER2 binding proteins that bind in the extra-cellular domain (ECD). In various embodiments, the binding proteins of the invention bind in the LR1, CR1, LR2 or CR2 domain of the ECD. Unlike HERCEPTIN®, in some embodiments the binding proteins of the invention preferentially bind ErbB2 nomodimers over monomers or shed ECD. In some embodiments, the binding proteins of the invention bind ECD homodimers substantially more than monomers. In some cases, the binding protein has no appreciable or significant binding to ECD monomers or to shed ECD.

**[0056]** In some embodiments, the novel binding proteins are ErbB2 agonists and increase tyrosine phosphorylation of ErbB2, and at the same time, have anti-proliferative activity and pro-apoptotic activity.

[0057] The anti-ErbB2/HER2 binding proteins of the invention can be obtained by any of numerous methods known to those skilled in the art. For example, antibodies can be produced using recombinant DNA methods (U.S. Pat. No. 4,816,567). Monoclonal antibodies may be produced by generation of hybridomas (see e.g., Kohler and Milstein (1975) Nature, 256: 495-499) in accordance with known methods. Hybridomas formed in this manner are then screened using standard methods, such as enzyme-linked immunosorbent assay (ELISA) and surface plasmon resonance (BIA-CORETM) analysis, to identify one or more hybridomas that produce an antibody that specifically binds with a specified antigen. Any form of the specified antigen may be used as the immunogen, e.g., recombinant antigen, naturally occurring forms, any variants or fragments thereof, as well as antigenic peptide thereof.

**[0058]** One exemplary method of making antibodies includes screening protein expression libraries, e.g., phage or ribosome display libraries. Phage display is described, for example, in Ladner et al., U.S. Pat. No. 5,223,409; Smith (1985) *Science* 228:1315-1317; Clackson et al. (1991) *Nature*, 352: 624-628; Marks et al. (1991) *J. Mol. Biol.*, 222: 581-597WO 92/18619; WO 91/17271; WO 92/20791; WO 92/15679; WO 93/01288; WO 92/01047; WO 92/09690; and WO 90/02809.

**[0059]** In addition to the use of display libraries, the specified antigen can be used to immunize a non-human animal, e.g., a rodent, e.g., a mouse, hamster, or rat. In one embodiment, the non-human animal includes at least a part of a human immunoglobulin gene. For example, it is possible to engineer mouse strains deficient in mouse antibody production with large fragments of the human Ig loci. Using the hybridoma technology, antigen-specific monoclonal antibodies derived from the genes with the desired specificity may be produced and selected. See, e.g., XENOMOUSETM, Green et al. (1994) *Nature Genetics* 7:13-21, US 2003-0070185, WO 96/34096, published Oct. 31, 1996, and PCT Application No. PCT/US96/05928, filed Apr. 29, 1996.

**[0060]** The subunit structures, e.g., a  $C_{H}$ ,  $V_{H}$ ,  $C_{L}$ ,  $V_{L}$ , CDR, FR, and three-dimensional configurations of different classes of immunoglobulins are well known in the art. For a review of the antibody structure, see *Antibodies: A Laboratory Manual*, *Cold Spring Harbor Laboratory*, eds. Harlow et al., 1988. One of skill in the art will recognize that a complete 4-chain immunoglobulin comprises active portions, e.g., a portion of the  $V_H$  or  $V_L$  domain or a CDR that binds to the antigen, i.e., an antigen-binding fragment, or, e.g., the portion of the  $C_H$  subunit that binds to and/or activates, e.g., an Fc receptor and/or complement. CDRs typically refer to regions that are hypervariable in sequence and/or form structurally defined

loops, for example, Kabat CDRs are based on sequence variability, as described in Sequences of Proteins of Immunological Interest, US Department of Health and Human Services (1991), eds. Kabat et al, or alternatively, to the location of the hypervariable structural loops as described by Chothia. See, e.g., Chothia, D. et al. (1992) J. Mol. Biol. 227:799-817; and Tomlinson et al. (1995) EMBOJ. 14:4628-4638. Still another standard is the AbM definition used by Oxford Molecular's AbM antibody modelling software, which defines the contact hypervariable regions based on crystal structure. See, generally, e.g., Protein Sequence and Structure Analysis of Antibody Variable Domains. In: Antibody Engineering Lab Manual (Ed.: Duebel, S, and Kontermann, R., Springer-Verlag, Heidelberg). Embodiments described with respect to Kabat CDRs can alternatively be implemented using similar described relationships with respect to Chothia hypervariable loops or to the AbM-defined loops.

[0061] In another embodiment, a monoclonal antibody is obtained from the non-human animal, and then modified, e.g., humanized, deimmunized, chimeric, may be produced using recombinant DNA techniques known in the art. A variety of approaches for making chimeric antibodies have been described. See e.g., Morrison et al., Proc. Natl. Acad. Sci. U.S.A. 81:6851, 1985; Takeda et al., Nature 314:452, 1985, Cabilly et al., U.S. Pat. No. 4,816,567; Boss et al., U.S. Pat. No. 4,816,397; Tanaguchi et al., European Patent Publication EP171496; European Patent Publication 0173494, United Kingdom Patent GB 2177096B. Humanized antibodies may also be produced, for example, using transgenic mice that express human heavy and light chain genes, but are incapable of expressing the endogenous mouse immunoglobulin heavy and light chain genes. Winter describes an exemplary CDRgrafting method that may be used to prepare the humanized antibodies described herein (U.S. Pat. No. 5,225,539). All of the CDRs of a particular human antibody may be replaced with at least a portion of a non-human CDR, or only some of the CDRs may be replaced with non-human CDRs. It is only necessary to replace the number of CDRs required for binding of the humanized antibody to a predetermined antigen.

[0062] Humanized antibodies or fragments thereof can be generated by replacing sequences of the Fv variable domain that are not directly involved in antigen binding with equivalent sequences from human Fv variable domains. Exemplary methods for generating humanized antibodies or fragments thereof are provided by Morrison (1985) Science 229:1202-1207; by Oi et al. (1986) BioTechniques 4:214; and by U.S. Pat. No. 5,585,089; U.S. Pat. No. 5,693,761; U.S. Pat. No. 5,693,762; U.S. Pat. No. 5,859,205; and U.S. Pat. No. 6,407, 213. Those methods include isolating, manipulating, and expressing the nucleic acid sequences that encode all or part of immunoglobulin Fv variable domains from at least one of a heavy or light chain. Such nucleic acids may be obtained from a hybridoma producing an antibody against a predetermined target, as described above, as well as from other sources. The recombinant DNA encoding the humanized antibody molecule can then be cloned into an appropriate expression vector.

**[0063]** In certain embodiments, a humanized antibody is optimized by the introduction of conservative substitutions, consensus sequence substitutions, germline substitutions and/or backmutations. Such altered immunoglobulin molecules can be made by any of several techniques known in the art, (e.g., Teng et al., *Proc. Natl. Acad. Sci. U.S.A.*, 80: 7308-7312, 1983; Kozbor et al., *Immunology Today*, 4: 7279, 1983;

Olsson et al., *Meth. Enzymol.*, 92: 3-16, 1982), and may be made according to the teachings of PCT Publication WO92/06193 or EP 0239400).

[0064] An antibody or fragment thereof may also be modified by specific deletion of human T cell epitopes or "deimmunization" by the methods disclosed in WO 98/52976 and WO 00/34317. Briefly, the heavy and light chain variable domains of an antibody can be analyzed for peptides that bind to MHC Class II; these peptides represent potential T-cell epitopes (as defined in WO 98/52976 and WO 00/34317). For detection of potential T-cell epitopes, a computer modeling approach termed "peptide threading" can be applied, and in addition a database of human MHC class II binding peptides can be searched for motifs present in the  $V_H$  and  $V_L$ sequences, as described in WO 98/52976 and WO 00/34317. These motifs bind to any of the 18 major MHC class II DR allotypes, and thus constitute potential T cell epitopes. Potential T-cell epitopes detected can be eliminated by substituting small numbers of amino acid residues in the variable domains, or preferably, by single amino acid substitutions. Typically, conservative substitutions are made. Often, but not exclusively, an amino acid common to a position in human germline antibody sequences may be used. Human germline sequences, e.g., are disclosed in Tomlinson, et al. (1992) J. Mol. Biol. 227:776-798; Cook, G. P. et al. (1995) Immunol. Today Vol. 16 (5): 237-242; Chothia, D. et al. (1992) J. Mol. Biol. 227:799-817; and Tomlinson et al. (1995) EMBO J. 14:4628-4638. The V BASE directory provides a comprehensive directory of human immunoglobulin variable region sequences (compiled by Tomlinson, I. A. et al. MRC Centre for Protein Engineering, Cambridge, UK). These sequences can be used as a source of human sequence, e.g., for framework regions and CDRs. Consensus human framework regions can also be used, e.g., as described in U.S. Pat. No. 6,300,064.

[0065] In certain embodiments, an antibody can contain an altered immunoglobulin constant or Fc region. For example, an antibody produced in accordance with the teachings herein may bind more strongly or with more specificity to effector molecules such as complement and/or Fc receptors, which can control several immune functions of the antibody such as effector cell activity, lysis, complement-mediated activity, antibody clearance, and antibody half-life. Typical Fc receptors that bind to an Fc region of an antibody (e.g., an IgG antibody) include, but are not limited to, receptors of the FcyRI, FcyRII, and FcyRIII and FcRn subclasses, including allelic variants and alternatively spliced forms of these receptors. Fc receptors are reviewed in Ravetch and Kinet, Annu. Rev. Immunol 9:457-92, 1991; Capel et al., Immunomethods 4:25-34, 1994; and de Haas et al., J. Lab. Clin. Med. 126:330-41, 1995).

**[0066]** For additional antibody production techniques, see Antibodies: A Laboratory Manual, eds. Harlow et al., Cold Spring Harbor Laboratory, 1988. The present invention is not necessarily limited to any particular source, method of production, or other special characteristics of an antibody.

**[0067]** In some embodiments, an anti-ErbB2 antibody of the invention may be a  $V_{HH}$  molecule.  $V_{HH}$  molecules (or nanobodies), as known to the skilled artisan, are heavy chain variable domains derived from immunoglobulins naturally devoid of light chains, such as those derived from Camelidae as described in WO9404678, incorporated herein by reference. Such a VHH molecule can be derived from antibodies raised in Camelidae species, for example in camel, llama,

dromedary, alpaca and guanaco and is sometomes called a camelid or camelized variable domain. See e.g., Muyldermans., J. Biotechnology (2001) 74(4):277-302, incorporated herein by reference. Other species besides Camelidae may produce heavy chain antibodies naturally devoid of light chain.  $V_{HH}$  molecules are about 10 times smaller than IgG molecules. They are single polypeptides in which the CDR3 is longer than a conventional antibody, the VH:VL interface residues are different, and extra cysteines are generally present. These molecules tend to be very stable, resisting extreme pH and temperature conditions. Moreover, they are resistant to the action of proteases which is not the case for conventional antibodies. Furthermore, in vitro expression of  $V_{HH}$ s produces high yield, properly folded functional  $V_{HH}$ s. In addition, antibodies generated in Camelids will recognize epitopes other than those recognized by antibodies generated in vitro through the use of antibody libraries or via immunization of mammals other than Camelids (see WO 9749805, that is incorporated herein by reference). In additional embodiments, an anti-ErbB2 antibodies or binding fragments of the invention may include single domain antibodies such as immunoglobulin new antigen receptors (IgNARs), which are a unique group of antibody isotypes found in the serum of sharks (Greenberg et al., Nature 374: 168-173 (1995); Nuttall et al., Mol. Immunol., 38: 313-326. (2001)). These are bivalent molecules, targeting antigen through a single immunoglobulin variable domain (~13 kDa) displaying two complementarity determining region (CDR) loops (Roux et al., Proc. Natl. Acad. Sci., 95: 11804-11809 (1998)) and having unusually long and structurally complex CDR3s, which display a high degree of variability (Greenberg et al., 1995).

[0068] Antibodies, also known as immunoglobulins, are typically tetrameric glycosylated proteins composed of two light (L) chains of approximately 25 kDa each and two heavy (H) chains of approximately 50 kDa each. Two types of light chain, termed lambda and kappa, may be found in antibodies. Depending on the amino acid sequence of the constant domain of heavy chains, immunoglobulins can be assigned to five major classes: A, D, E, G, and M, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. Each light chain includes an N terminal variable (V) domain  $(V_I)$  and a constant (C) domain  $(C_L)$ . Each heavy chain includes an N terminal V domain  $(V_H)$ , three or four C domains  $(C_Hs)$ , and a hinge region collectively referred to as the constant region of the heavy chain. The  $C_H$  domain most proximal to  $V_H$  is designated as  $C_H 1$ . The  $V_H$  and  $V_L$  domains consist of four regions of relatively conserved sequences called framework regions (FR1, FR2, FR3, and FR4), that form a scaffold for three regions of hypervariable sequences also referred to as complementarity determining regions CDRs. CDRs are referred to as CDR1, CDR2, and CDR3. Accordingly, CDR constituents on the heavy chain may be referred to as HCDR1, HCDR2, and HCDR3, while CDR constituents on the light chain are referred to as LCDR1, LCDR2, and LCDR3. CDR3 is typically the greatest source of molecular diversity within the antibody-binding site.

**[0069]** The anti-ErbB2 binding proteins of the invention include complete 4-chain antibodies and antigen-binding fragments of complete antibodies. An antigen-binding fragment (also referred to as an antigen-binding portion) includes but is not limited to Fab, Fv and ScFv molecules. The Fab fragment (Fragment antigen-binding) consists of  $V_{H}$ - $C_{H}$ 1 and  $V_{L}$ - $C_{L}$  domains covalently linked by a disulfide bond

between the constant regions. The  $F_v$  fragment is smaller and consists of  $V_H$  and  $V_L$  domains non-covalently linked. To overcome the tendency of non-covalently linked domains to dissociate, a single chain  $F_v$  fragment (scF_v) can be constructed. The scFv contains a flexible polypeptide that links (1) the C-terminus of  $V_H$  to the N-terminus of  $V_L$ , or (2) the C-terminus of  $V_L$  to the N-terminus of  $V_H$ . Repeating units of (Gly₄Ser)—often 3 or 4 repeats may be used as a linker, but other linkers are known in the art.

**[0070]** A "bispecific" or "bifunctional antibody" is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai & Lachmann, *Clin. Exp. Immunol.* 79:315-321 (1990); Kostelny et al., *J. Immunol.* 148, 1547-1553 (1992). In one embodiment, the bispecific antibody comprises a first binding domain polypeptide, such as a Fab' fragment, linked via an immunoglobulin constant region to a second binding domain polypeptide.

**[0071]** In some embodiments, an anti-ErbB2 binding protein of the invention is a Small Modular ImmunoPharmaceuticals (SMIPTM). SMIPs and their uses and applications are disclosed in, e.g., U.S. Published Patent Application. Nos. 2003/0118592, 2003/0133939, 2004/0058445, 2005/0136049, 2005/0175614, 2005/0180970, 2005/0186216, 2005/0202012, 2005/020203, 2005/0202028, 2005/0202534, and 2005/0238646, and related patent family members thereof, all of which are hereby incorporated by reference herein in their entireties.

A SMIPTM typically refers to a binding domain-immunoglobulin fusion protein that includes a binding domain polypeptide that is fused or otherwise connected to an immunoglobulin hinge or hinge-acting region polypeptide, which in turn is fused or otherwise connected to a region comprising one or more native or engineered constant regions from an immunoglobulin heavy chain, other than  $C_H 1$ , for example, the  $C_H 2$ and  $C_H3$  regions of IgG and IgA, or the  $C_H3$  and  $C_H4$  regions of IgE (see e.g., U.S. 2005/0136049 by Ledbetter, J. et al., which is incorporated by reference, for a more complete description). The binding domain-immunoglobulin fusion protein can further include a region that includes a native or engineered immunoglobulin heavy chain C_H2 constant region polypeptide (or  $C_H$ 3 in the case of a construct derived in whole or in part from IgE) that is fused or otherwise connected to the hinge region polypeptide and a native or engineered immunoglobulin heavy chain C_H3 constant region polypeptide (or  $C_{\mu}4$  in the case of a construct derived in whole or in part from IgE) that is fused or otherwise connected to the  $C_H 2$  constant region polypeptide (or  $C_H 3$  in the case of a construct derived in whole or in part from IgE). Typically, such binding domain-immunoglobulin fusion proteins are capable of at least one immunological activity selected from the group consisting of antibody dependent cell-mediated cytotoxicity, complement fixation, and/or binding to a target, for example, a target antigen, such as human ErbB2.

**[0072]** The binding domain of a SMIP of the invention may contain a complete  $V_H$  and a complete  $V_L$  joined by linker antigen-binding portions of a  $V_H$  and/or  $V_L$  and may V2 or be linked in either orientation, i.e.,  $V_H$ -linker- $V_L$  or  $V_L$ -linker- $V_H$ -Any suitable linker can be used in a SMIP of the invention and will be known to those of skill in the art. Exemplary linkers may be found, for example in WO 2007/146968

Tables 5 and 10-12 of which are incorporated by reference in their entirety. Likewise, any immunoglobulin hinge sequence or hinge-acting sequence may be used in a SMIP of the invention.

**[0073]** In some SMIP embodiments at least one of the immunoglobulin heavy chain constant region polypeptides (i.e., CH2, CH3 or CH4) is from a human immunoglobulin heavy chain. In various embodiments, the immunoglobulin heavy chain constant region polypeptides are of an isotype selected from human IgG and human IgA. In certain further embodiments of the above described SMIP, the linker polypeptide comprises at least one polypeptide having as an amino acid sequence (Gly₄, Ser) and in certain other embodiments the linker polypeptide. In certain embodiments the immunoglobulin hinge region polypeptide.

[0074] An immunoglobulin hinge region polypeptide, as discussed above, includes any hinge peptide or polypeptide that occurs naturally, as an artificial peptide or as the result of genetic engineering and that is situated in an immunoglobulin heavy chain polypeptide between the amino acid residues responsible for forming intrachain immunoglobulin-domain disulfide bonds in CH1 and CH2 regions; hinge region polypeptides for use in the present invention may also include a mutated hinge region polypeptide. Accordingly, an immunoglobulin hinge region polypeptide may be derived from, or may be a portion or fragment of (i.e., one or more amino acids in peptide linkage, typically 5-65 amino acids, preferably 10-50, more preferably 15-35, still more preferably 18-32, still more preferably 20-30, still more preferably 21, 22, 23, 24, 25, 26, 27, 28 or 29 amino acids) an immunoglobulin polypeptide chain region classically regarded as having hinge function, as described above. But, a hinge region polypeptide for use in the instant invention need not be so restricted and may include amino acids situated (according to structural criteria for assigning a particular residue to a particular domain that may vary, as known in the art) in an adjoining immunoglobulin domain such as a CH1 domain or a CH2 domain, or in the case of certain artificially engineered immunoglobulin constructs, an immunoglobulin variable region domain.

[0075] Wild-type immunoglobulin hinge region polypeptides include any naturally occurring hinge region that is located between the constant region domains, CH1 and CH2, of an immunoglobulin. The wild-type immunoglobulin hinge region polypeptide is preferably a human immunoglobulin hinge region polypeptide, preferably comprising a hinge region from a human IgG immunoglobulin, and more preferably, a hinge region polypeptide from a human IgG1 isotype. As is known to the art, despite the tremendous overall diversity in immunoglobulin amino acid sequences, immunoglobulin primary structure exhibits a high degree of sequence conservation in particular portions of immunoglobulin polypeptide chains, notably with regard to the occurrence of cysteine residues which, by virtue of their sulfyhydryl groups, offer the potential for disulfide bond formation with other available sulfhydryl groups. Accordingly, in the context of the present invention wild-type immunoglobulin hinge region polypeptides may be regarded as those that feature one or more highly conserved (e.g., prevalent in a population in a statistically significant manner) cysteine residues, and in certain preferred embodiments a mutated hinge region polypeptide may be selected that contains zero or one cysteine residue and that is derived from such a wild-type hinge region.

**[0076]** A mutated immunoglobulin hinge region polypeptide may comprise a hinge region that has its origin in an immunoglobulin of a species, of an immunoglobulin isotype or class, or of an immunoglobulin subclass that is different from that of the CH2 and CH3 domains. For instance, in certain embodiments of the invention, the SMIP may comprise a binding domain polypeptide that is fused to an immunoglobulin hinge region polypeptide comprising a wild-type human IgA hinge region polypeptide, or a mutated human IgA hinge region polypeptide that contains zero or only one cysteine residues, as described herein. Such a hinge region polypeptide may be fused to an immunoglobulin heavy chain CH2 region polypeptide from a different Ig isotype or class, for example an IgG subclass, which in certain preferred embodiments will be the IgG1 subclass.

[0077] In some embodiments, an anti-ErbB2 antibody of the invention is a  $\mathrm{V}_{H\!H}$  molecule.  $\mathrm{V}_{H\!H}$  molecules (or nanobodies), as known to the skilled artisan, are heavy chain variable domains derived from immunoglobulins naturally devoid of light chains, such as those derived from Camelidae as described in WO9404678, incorporated herein by reference. Such a  $V_{HH}$  molecule can be derived from antibodies raised in Camelidae species, for example in camel, llama, dromedary, alpaca and guanaco and is sometomes called a camelid or camelized variable domain. See e.g., Muyldermans., J. Biotechnology (2001) 74(4):277-302, incorporated herein by reference. Other species besides Camelidae may produce heavy chain antibodies naturally devoid of light chain.  $V_{HH}$  molecules are about 10 times smaller than IgG molecules. They are single polypeptides and very stable, resisting extreme pH and temperature conditions. Moreover, they are resistant to the action of proteases which is not the case for conventional antibodies. Furthermore, in vitro expression of V_{HH}s produces high yield, properly folded functional  $V_{HH}$ s. In addition, antibodies generated in Camelids will recognize epitopes other than those recognized by antibodies generated in vitro through the use of antibody libraries or via immunization of mammals other than Camelids (see WO 9749805, that is incorporated herein by reference).

[0078] Amino acid (AA) sequences of illustrative heavy chain variable domains  $(V_H)$  and light chain variable domains  $(V_L)$  of the anti-ErbB2 antibodies of this invention, are set forth in the attached Sequence Table. Table 1 provides the Sequence Identifiers (SEQ ID Nos) of the  $V_H$  and  $V_T$ domains. Thirty-one specific embodiments of the antibodies are identified as: S1R2A_CS_1F7, S1R2A_CS_1D11, S1R2C_CS_1D3, S1R2C_CS_1H12, S1R2A_CS_1D3, S1R3B2_BMV_1E1, S1R3C1_CS_1D3, S1R3B2_DP47_ 1E8, S1R3B2 BMV 1G2, S1R3B2 BMV 1H5, S1R3C1_CS_1A6, S1R3B2_DP47_1C9, S1R3B2_DP47_ 1E10, S1R3C1_CS_1B10, S1R3A1_BMV_1F3, S1R3B1_ BMV_1G11, S1R3A1_BMV_1G4, S1R3B1_BMV_ 1H11, S1R3A1_CS_1B9, S1R3B1_BMV_1H9, S1R3A1_ CS_1B10, S1R3B1_BMV_1C12, S1R3C1_BMV_1H11, S1R3B1_BMV_1A10, S1R3A1_CS_1D11, S1R3C1_ DP47_1H1, S1R3A1_CS_1B12, S1R3B1_BMV_1H5, S1R3A1_DP47_1A6, S1R3B1_DP47_1E1 and S1R3B1_ BMV_1A1.

TABLE 1			
HUMAN ANTI-E	rbB2 BINDING DOMAINS		

		SEQUENCE IDENTIFIER (SEQ ID Nos:) Variable Domain Protein Sequences		
scFv	Heavy	Light		
S1R2A_CS_1F7	1	2 and 63		
S1R2A_CS_1D11	3	4 and 64		
S1R2C_CS_1D3	5 and 65	6 and 66		
S1R2C_CS_1H12	7 and 67	8 and 68		
S1R2A_CS_1D3	9	10 and 69		
S1R3B2_BMV_1E1	11	12 and 70		
S1R3C1_CS_1D3	13	14 and 71		
S1R3B2_DP47_1E8	15	16 and 72		
S1R3B2_BMV_1G2	17	18 and 73		
S1R3B2_BMV_1H5	19	20 and 74		
S1R3C1_CS_1A6	21	22 and 75		
S1R3B2_DP47_1C9	23	24 and 76		
S1R3B2_DP47_1E10	25	26 and 77		
S1R3C1_CS_1B10	27	28 and 78		
S1R3A1_BMV_1F3	29	30 and 79		
S1R3B1_BMV_1G11	31	32 and 80		
S1R3A1_BMV_1G4	33	34 and 81		
S1R3B1_BMV_1H11	35	36 and 82		
S1R3A1_CS_1B9	37	38 and 83		
S1R3B1_BMV_1H9	39	40 and 84		
S1R3A1_CS_1B10	41	42 and 85		
S1R3B1_BMV_1C12	43	44 and 86		
S1R3C1_BMV_1H11	45	46 and 87		
S1R3B1_BMV_1A10	47	48 and 88		
S1R3A1_CS_1D11	49	50 and 89		
S1R3C1_DP47_1H1	51	52 and 90		
S1R3A1_CS_1B12	53	54 and 91		
S1R3B1_BMV_1H5	55	56 and 92		
S1R3A1_DP47_1A6	57	58 and 93		
S1R3B1_DP47_1E1	59	60 and 94		
S1R3B1_BMV_1A1	61	62 and 95		

**[0079]** According to the nomenclature used herein, "S1R2A_CS_1F7" indicates clone 1F7 from round 2A of the first selection from the CS library.

**[0080]** An anti-ErbB2 binding protein of this invention may optionally comprise antibody constant regions or parts thereof. For example, a  $V_L$  domain may be attached at its C-terminal end to a light chain constant domain which can be a C $\kappa$  or a C $\lambda$ . Similarly, a  $V_H$  domain or portion thereof may be attached to all or part of a heavy chain constant region, which can be a IgA, IgD, IgE, IgG, or IgM constant region or any isotype subclass including IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2. Constant region sequences are known in the art (see, for example, Kabat et al., Sequences of Proteins of Immunological Interest, No. 91-3242, National Institutes of Health Publications, Bethesda, Md. (1991)). Therefore, binding proteins within the scope of this invention may include  $V_H$  and  $V_L$  domains, or a portion thereof, combined with constant regions or portions thereof known in the art.

[0081] In certain embodiments of the invention, the ErbB2 binding protein comprises a  $\mathbf{V}_{\!H}$  domain, a  $\mathbf{V}_{\!L}$  domain, or a combination thereof, comprising the  $\mathbf{V}_{\!H}$  or  $\mathbf{V}_{\!L}$  amino acid sequence, respectively, found in any one of S1R2A_CS_ 1F7, S1R2A_CS_1D11, S1R2C_CS_1D3, S1R2C_CS_ 1H12, S1R2A_CS_1D3, S1R3B2_BMV_1E1, S1R3C1_ CS_1D3, S1R3B2_DP47_1E8, S1R3B2_BMV_1G2, S1R3C1_CS_1A6, S1R3B2_BMV_1H5, S1R3B2_ DP47_1C9, S1R3B2_DP47_1E10, S1R3C1_CS_1B10, S1R3A1_BMV_1F3, S1R3B1_BMV_1G11, S1R3A1_ BMV_1G4, S1R3B1_BMV_1H11, S1R3A1_CS_1B9, S1R3B1_BMV_1H9, S1R3A1_CS_1B10, S1R3B1

**[0082]** An anti-ErbB2 antibody of the invention may comprise one, two, three, four, five or all six complementarity determining regions (CDRs) from any one of the above-listed antibodies. In some embodiments, an anti-ErbB2 binding protein of the invention comprises the HCDR1, HCDR2 and HCDR3 (heavy chain CDR set), the LCDR1, LCDR2 and LCDR3 (light chain CDR set) or both the heavy chain CDR set and the light chain CDR set of one of the thirty-one antibodies exemplified herein.

[0083] A CDR3 sequence found in any one of the thirty-one specifically exemplified antibodies are encompassed within the scope of this invention. For example, in one embodiment, an anti-ErbB2 binding protein of the invention comprises an HCDR3 amino acid sequence found in any one of S1R2A_ CS_1F7, S1R2A_CS_1D11, S1R2C_CS_1D3, S1R2C_ S1R2A CS 1D3, CS 1H12, S1R3B2 BMV 1E1, S1R3C1_CS_1D3, S1R3B2_DP47_1E8, S1R3B2_BMV 1G2, S1R3B2_BMV_1H5, S1R3C1_CS_1A6, S1R3B2_ DP47_1C9, S1R3B2_DP47_1E10, S1R3C1_CS_1B10, S1R3A1_BMV_1F3, S1R3B1_BMV_1G11, S1R3A1_ BMV_1G4, S1R3B1_BMV_1H11, S1R3A1_CS_1B9, S1R3B1_BMV_1H9, S1R3A1_CS_1B10, S1R3B1_ BMV_1C12, S1R3C1_BMV_1H11, S1R3B1_BMV_ S1R3C1_DP47_1H1, 1A10. S1R3A1_CS_1D11, S1R3A1_CS_1B12, S1R3B1_BMV_1H5, S1R3A1_ DP47_1A6, S1R3B1_DP47_1E1 or S1R3B1_BMV_1A1. [0084] In certain embodiments, the  $V_{II}$  and/or  $V_{I}$  domains may be germlined, i.e., the framework regions (FR) of these domains are mutated using conventional molecular biology techniques to match the germline sequence. In other embodiments, the FR sequences remain diverged from the consensus germline sequences.

**[0085]** In one embodiment, mutagenesis is used to make an antibody more similar to one or more germline sequences. This may be desirable when mutations are introduced into the framework region of an antibody through somatic mutagenesis or through error prone PCR. Germline sequences for the  $V_H$  and  $V_L$  domains can be identified by performing amino acid and nucleic acid sequence alignments against the VBASE database (MRC Center for Protein Engineering, UK). VBASE is a comprehensive directory of all human germline variable region sequences compiled from over a thousand published sequences, including those in the current releases of the Genbank and EMBL data libraries. In some embodiments, the FR regions of the scFvs are mutated in conformity with the closest matches in the VBASE database and the CDR portions are kept intact.

**[0086]** In certain embodiments, an anti-ErbB2 binding of this invention specifically binds the same epitope as, competes with or cross-competes with an antibody selected from the group consisting of: S1R2A_CS_1F7, S1R2A_CS_1D11, S1R2C_CS_1D3, S1R2C_CS_1H12, S1R2A_CS_1D3, S1R3B2_BMV_1E1, S1R3C1_CS_1D3, S1R3B2_DP47_1E8, S1R3B2_BMV_1G2, S1R3B2_BMV_1H5, S1R3C1_CS_1A6, S1R3B2_DP47_1C9, S1R3B2_DP47_1E10, S1R3C1_CS_1B10, S1R3A1_BMV_1F3, S1R3B1_

BMV_1G11, S1R3A1_BMV_1G4, S1R3B1_BMV_ 1H11, S1R3A1_CS_1B9, S1R3B1_BMV_1H9, S1R3A1_ CS_1B10, S1R3B1_BMV_1C12, S1R3C1_BMV_1H11, S1R3B1_BMV_1A10, S1R3A1_CS_1D11, S1R3C1_ DP47_1H1, S1R3A1_CS_1B12, S1R3B1_BMV_1H5, S1R3A1_DP47_1A6, S1R3B1_DP47_1E1 and S1R3B1_ BMV_1A1, for binding to ErbB2. In some embodiments, such competing or ErbB2-mediated cross-competing binding protein is an ErbB2 agonist and may further reduce proliferation of a cancer call, reduce the rate of growth of an ErbB2expressing tumor and/or increases apoptosis in such cells and tumors. In some embodiments, such competing or crosscompeting binding proteins bind ErbB2 ECD homo-dimers but do not bind ECD monomers or shed ECD.

[0087] Such antibodies can be identified in a competitive binding assay. One can determine whether an antibody binds to the same epitope or cross competes for binding with a binding protein of the invention antibody by using methods known in the art. In one embodiment, one allows the binding protein of the invention to bind to ErbB2 under saturating conditions and then measures the ability of the test protein to bind to the ECD. If the test antibody is able to bind to the ECD at the same time as the reference binding protein, then the test antibody binds to a different epitope than the reference binding protein. However, if the test protein is not able to bind the to the ECD at the same time, then the test protein binds to the same epitope, an overlapping epitope, or an epitope that is in close proximity to the epitope bound by the binding protein of the invention. This experiment can be performed using ELISA, RIA, BIACORE™, or flow cytometry. To test whether a binding protein cross-competes with another anti-ErbB2 binding protein, one may use the competition method described above in two directions, i.e. determining if the known binder blocks the test binder and vice versa. In a preferred embodiment, the experiment is performed using BIACORETM.

**[0088]** In one embodiment, the association constant  $(K_A)$  of an ErbB2 binding protein of the invention is at least  $10^6 \text{ M}^{-1}$ . In another embodiment, the association constant of these antibodies for human ErbB2 is at least  $10^9 \text{ M}^{-1}$ . In other embodiments, the association constant of these antibodies for human ErbB2 is at least  $10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , or at least  $10^{12} \text{ M}^{-1}$ . The binding affinity may be determined using techniques known in the art, such as ELISA, biosensor technology, such as biospecific interaction analysis, or other techniques including those described in this application.

**[0089]** In addition to sequence homology analyses, epitope mapping (see, e.g., Epitope Mapping Protocols, ed. Morris, Humana Press, 1996), and secondary and tertiary structure analyses can be carried out to identify specific 3D structures assumed by the presently disclosed antibodies and their complexes with antigens. Such methods include, but are not limited to, X-ray crystallography (Engstom (1974) Biochem. Exp. Biol., 11:7-13) and computer modeling of virtual representations of the present antibodies (Fletterick et al. (1986) Computer Graphics and Molecular Modeling, in Current Communications in Molecular Biology, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.).

**[0090]** The invention further provides anti-ErbB2 binding proteins that comprise altered  $V_H$  and/or  $V_L$  sequence(s) compared to the sequences in Table 1. Such binding proteins may be produced by a skilled artisan using techniques well-known in the art. For example, amino acid substitutions, deletions, or additions can be introduced in FR and/or CDR regions. FR

changes are usually designed to improve the stability and immunogenicity of the antibody, while CDR changes are typically designed to increase antibody affinity for its antigen. The changes that increase affinity may be tested by altering CDR sequence and measuring antibody affinity for its target (see Antibody Engineering, 2nd ed., Oxford University Press, ed. Borrebaeck, 1995).

**[0091]** Antibodies whose CDR sequences differ insubstantially from those found in any one of thirty-one specifically exemplified antibodies are encompassed within the scope of this invention. Typically, this involves substitution of an amino acid with an amino acid having similar charge, hydrophobic, or stereochemical characteristics. More drastic substitutions in FR regions, in contrast to CDR regions, may also be made as long as they do not adversely affect (e.g., reduce affinity by more than 50% as compared to unsubstituted antibody) the binding properties of the binding protein. Substitutions may also be made to germine the binding protein or stabilize the antigen binding site.

**[0092]** Conservative modifications will produce molecules having functional and chemical characteristics similar to those of the molecule from which such modifications are made. In contrast, substantial modifications in the functional and/or chemical characteristics of the molecules may be accomplished by selecting substitutions in the amino acid sequence that differ significantly in their effect on maintaining (1) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (2) the charge or hydrophobicity of the molecule at the target site, or (3) the size of the molecule.

**[0093]** For example, a "conservative amino acid substitution" may involve a substitution of a native amino acid residue with a normative residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position. (See, for example, MacLennan et al., 1998, Acta Physiol. Scand. Suppl. 643:55-67; Sasaki et al., 1998, Adv. Biophys. 35:1-24).

**[0094]** Desired amino acid substitutions (whether conservative or non-conservative) can be determined by those skilled in the art at the time such substitutions are desired. For example, amino acid substitutions can be used to identify important residues of the molecule sequence, or to increase or decrease the affinity of the molecules described herein. Exemplary amino acid substitutions include, but are not limited to, those set forth in Table 2.

TABLE 2

	Amino Acid Substitutions			
Original Residues	Exemplary Substitutions	More Conservative Substitutions		
Ala (A)	Val, Leu, Ile	Val		
Arg (R)	Lys, Gln, Asn	Lys		
Asn (N)	Gln	Gln		
Asp (D)	Glu	Glu		
Cys (C)	Ser, Ala	Ser		
Gln (Q)	Asn	Asn		
Gly (G)	Pro, Ala	Ala		
His (H)	Asn, Gln, Lys, Arg	Arg		
Ile (I)	Leu, Val, Met, Ala, Phe, Norleucine	Leu		
Leu (L)	Norleucine, Ile, Val, Met, Ala, Phe	Ile		
Lys (K)	Arg, 1,4 Diamino-butyric Acid, Gln, Asn	Arg		

TABLE 2-continued

	Amino Acid Substit	tutions
Original Residues	Exemplary Substitutions	More Conservative Substitutions
Met (M)	Leu, Phe, Ile	Leu
Phe (F)	Leu, Val, Ile, Ala, Tyr	Leu
Pro (P)	Ala	Gly
Ser (S)	Thr, Ala, Cys	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr, Phe	Tyr
Tyr (Y)	Trp, Phe, Thr, Ser	Phe
Val (V)	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

[0095] In certain embodiments, conservative amino acid substitutions also encompass non-naturally occurring amino acid residues that are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. [0096] In one embodiment, the method for making a variant  $V_{tr}$  domain comprises adding, deleting, or substituting at least

one amino acid in the disclosed  $V_H$  domains, and testing the variant  $V_H$  domain for ErbB2 binding or modulation of ErbB2 activity.

**[0097]** An analogous method for making a variant  $V_L$  domain comprises adding, deleting, or substituting at least one amino acid in the disclosed  $V_L$  domains, and testing the variant  $V_L$  domain for ErbB2 binding or modulation of ErbB2 activity.

**[0098]** A further aspect of the invention provides a method for preparing antibodies or antigen-binding fragments that specifically bind ErbB2. The method comprises:

**[0099]** (a) providing a starting repertoire of nucleic acids encoding a  $V_H$  domain that lacks at least one CDR or contains at least one CDR to be replaced;

**[0100]** (b) inserting into or replacing the CDR region of the starting repertoire with at least one donor nucleic acid encoding an amino acid sequence as substantially set out herein for a  $V_H$  CDR, yielding a product repertoire;

**[0101]** (c) expressing the nucleic acids of the product repertoire;

**[0102]** (d) selecting a specific antigen-binding fragment that binds to ErbB2; and

**[0103]** (e) recovering the specific antigen-binding fragment or nucleic acid encoding it.

**[0104]** In an analogous method, at least one  $V_L$  CDR of the invention is combined with a repertoire of nucleic acids encoding a  $V_L$  domain that lacks at least one CDR or contains at least one CDR to be replaced. The at least one  $V_H$  or  $V_L$  CDR may be a CDR1, a CDR2, a CDR3, or a combination thereof, found in any of the thirty-one specifically exemplified antibodies.

**[0105]** In one embodiment, the variable domain includes a CDR3 to be replaced or lacks a CDR3 encoding region and the at least one donor nucleic acid encodes a CDR3 amino acid sequence found in any one of SEQ ID Nos:1-62 or substantially as found in such sequence.

**[0106]** In another embodiment, the variable domain includes a CDR1 to be replaced or lacks a CDR1 encoding region and the at least one donor nucleic acid encodes a CDR1 amino acid sequence found in any one of SEQ ID Nos: 1-62. **[0107]** In another embodiment, the variable domain includes a CDR2 to be replaced or lacks a CDR2 encoding

region and the at least one donor nucleic acid encodes a CDR2 amino acid sequence found in any one of SEQ ID Nos: 1-62. **[0108]** In another embodiment, the variable domain includes a CDR3 to be replaced or lacks a CDR3 encoding region and further comprises a CDR1 to be replaced or lacks a CDR1 encoding region, where the at least one donor nucleic acid encodes a CDR3 a CDR1 amino acid sequence, respectively, found in any one of SEQ ID Nos: 1-62.

**[0109]** In another embodiment, the variable domain includes a CDR3 to be replaced or lacks a CDR3 encoding region and further comprises a CDR2 to be replaced or lacks a CDR2 encoding region, where the at least one donor nucleic acid encodes a CDR3 or CDR2 amino acid sequence, respectively, found in any one of SEQ ID Nos: 1-62.

**[0110]** In another embodiment, the variable domain includes a CDR3 to be replaced or lacks a CDR3 encoding region and further comprises a CDR1 and a CDR2 to be replaced or lacks a CDR1 and a CDR2 encoding region, where the at least one donor nucleic acid encodes CDR3, CDR1 or CDR2 amino acid sequence, respectively, found in any one of SEQ ID Nos: 1-62.

[0111] Using recombinant DNA methodology, a disclosed CDR sequence may be introduced into a repertoire of  $V_H$  or  $V_L$  domains lacking the respective CDR (Marks et al. (Bio-Technology (1992) 10: 779-783). For example, a primer adjacent to the 5' end of the variable domain and a primer to the third FR can be used to generate a repertoire of variable domain sequences lacking CDR3. This repertoire can be combined with a CDR3 of an antibody disclosed herein. Using analogous techniques, portions of a disclosed CDR sequence may be shuffled with portions of CDR sequences from other antibodies to provide a repertoire of antigen-binding fragments that bind ErbB2. Either repertoire can be expressed in a host system such as phage display (described in WO 92/01047 and its corresponding U.S. Pat. No. 5,969,108) so suitable antigen-binding fragments that bind to ErbB2 can be selected.

**[0112]** A further alternative uses random mutagenesis of a  $V_H$  or  $V_L$  sequence disclosed herein to generate variant  $V_H$  or  $V_L$  domains still capable of binding ErbB2. A technique using error-prone PCR is described by Gram et al. (Proc. Nat. Acad. Sci. U.S.A. (1992) 89: 3576-3580).

**[0113]** Another method uses direct mutagenesis of a  $V_H$  or  $V_L$  sequence disclosed herein. Such techniques are described by Barbas et al. (Proc. Nat. Acad. Sci. U.S.A. (1994) 91: 3809-3813) and Schier et al. (J. Mol. Biol. (1996) 263: 551-567).

[0114] Also encompassed by the invention is a portion of a variable domain that comprises at least one CDR region substantially as set out herein and, optionally, intervening framework regions from the  $V_H$  or  $V_L$  domains as set out herein. Variable domains lacking a portion of the N-terminus of the FR1 and/or a portion of the C, terminus of the FR4 are also encompassed by the invention. Additional residues at the N-terminal of the FR1 or C-terminal of the FR4 of the variable domain may not be the same residues found in naturally occurring antibodies. For example, construction of antibodies by recombinant DNA techniques often introduces N- or C-terminal residues from its use of linkers. Some linkers may be used to join variable domains to other variable domains (e.g., diabodies), constant domains, or proteinaceous labels. [0115] Although the embodiments specifically exemplified herein comprise a "matching" pair of  $V_H$  and  $V_L$  domains, a skilled artisan will recognize that alternative embodiments may comprise binding proteins containing only a single CDR from either  $V_L$  or  $V_H$  domain. Either one of the  $V_H$  domain or  $V_L$  domain can be used to screen for complementary domains capable of forming a two-domain specific binding protein capable of, binding to ErbB2 ECD. The screening may be accomplished by phage display screening methods using the so-called hierarchical dual combinatorial approach disclosed in WO 92/01047. In this approach, an individual colony containing either a H or L chain clone is used to infect a complete library of clones encoding the other chain (L or H), and the resulting two-chain specific antigen-binding domain is selected in accordance with phage display techniques as described.

[0116] In some alternative embodiments, the anti-ErbB2 binding protein can be linked to a protein (e.g., albumin) by chemical cross-linking or recombinant methods. The disclosed antibodies may also be linked to a variety of nonproteinaceous polymers (e.g., polyethylene glycol, polypropylene glycol, or polyoxyalkylenes) in manners set forth in U.S. Pat. No. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791, 192; or 4,179,337. The binding proteins can be chemically modified by covalent conjugation to a polymer, for example, to increase their half-life in blood circulation. Exemplary polymers and attachment methods are shown in U.S. Pat. Nos. 4,766,106; 4,179,337; 4,495,285; and 4,609,546. Binding proteins of the invention can be modified to alter their glycosylation; that is, at least one carbohydrate moiety can be deleted or added to the binding protein. Deletion or addition of glycosylation sites can be accomplished by changing amino acid sequence to delete or create glycosylation consensus sites, that are well known in the art. Another means of adding carbohydrate moieties is the chemical or enzymatic coupling of glycosides to amino acid residues of the antibody (see WO 87/05330 and Aplin et al. (1981) CRC Crit. Rev. Biochem., 22: 259-306). Removal of carbohydrate moieties can also be accomplished chemically or enzymatically (see Hakimuddin et al. (1987) Arch. Biochem. Biophys., 259: 52; Edge et al. (1981) Anal. Biochem., 118: 131; Thotakura et al. (1987) Meth. Enzymol., 138: 350).

**[0117]** Methods for altering an antibody constant region are known in the art. Antibodies with altered function (e.g., altered affinity for an effector ligand such as FcR on a cell or the C1 component of complement) can be produced by replacing at least one amino acid residue in the constant portion of the antibody with a different residue (see e.g., EP 388,151 A1, U.S. Pat. No. 5,624,821 and U.S. Pat. No. 5,648, 260). Similar types of alterations could be described that if applied to a murine or other species antibody would reduce or eliminate similar functions.

**[0118]** For example, it is possible to alter the affinity of an Fc region of an antibody (e.g., an IgG, such as a human IgG) for FcR (e.g., Fc gamma R1) or C1q. The affinity may be altered by replacing at least one specified residue with at least one residue having an appropriate functionality on its side chain, or by introducing a charged functional group, such as glutamate or aspartate, or perhaps an aromatic non-polar residue such as phenylalanine, tyrosine, tryptophan or alanine (see e.g., U.S. Pat. No. 5,624,821).

**[0119]** For example, replacing residue 297 (asparagine) with alanine in the IgG constant region significantly inhibits recruitment of effector cells, while only slightly reducing (about three fold weaker) affinity for Clq (see e.g., U.S. Pat. No. 5,624,821). The numbering of the residues in the heavy chain is that of the EU index (see Kabat et al., 1991 supra).

This alteration destroys the glycosylation site and it is believed that the presence of carbohydrate is required for Fc receptor binding. Any other substitution at this site that destroys the glycosylation site is believed to cause a similar decrease in lytic activity. Other amino acid substitutions, e.g., changing any one of residues 318 (Glu), 320 (Lys) and 322 (Lys), to Ala, are also known to abolish Clq binding to the Fc region of IgG antibodies (see e.g., U.S. Pat. No. 5,624,821). [0120] Modified binding proteins can be produced that have a reduced interaction with an Fc receptor. For example, it has been shown that in human IgG₃, which binds to the human Fc gamma R1 receptor, changing Leu 235 to Glu destroys its interaction with the receptor. Mutations on adjacent or close sites in the hinge link region of an antibody (e.g., replacing residues 234, 236 or 237 with Ala) can also be used to affect antibody affinity for the Fc gamma R1 receptor. The numbering of the residues in the heavy chain is based in the EU index (see Kabat et al., 1991 supra).

**[0121]** Additional methods for altering the lytic activity of an binding protein, for example, by altering at least one amino acid in the N-terminal region of the  $C_{H2}$  domain, are described in WO 94/29351 by Morgan et al. and U.S. Pat. No. 5,624,821.

**[0122]** One of skill in the art will appreciate that the modifications described above are not all-exhaustive, and that many other modifications are obvious to a skilled artisan in light of the teachings of the present disclosure.

**[0123]** A binding protein of this invention may be tagged with a detectable or functional label. These labels include radiolabels (e.g., ¹³¹I or ⁹⁹Tc), enzymatic labels (e.g., horse-radish peroxidase or alkaline phosphatase), and other chemical moieties (e.g., biotin).

[0124] In some embodiments, the invention features a human, monoclonal antibody that specifically binds the ECD, ErbB2, in particular, human ErbB2 and possesses one or more of the following characteristics: (1) it is an in vitro generated antibody (2) it is an in vivo generated antibody (e.g., transgenic mouse system); (3) it binds to ErbB2 with an association constant of at least  $10^{12}$  M⁻¹; (4) it binds to ErbB2 with an association constant of at least  $10^{11}$  M⁻¹; (5) it binds to ErbB2 with an association constant of at least  $10^{10}$  M⁻¹; (6) it binds to ErbB2 with an association constant of at least  $10^9$  $M^{-1}$ ; (7) it binds to ErbB2 with an association constant of at least  $10^6 \text{ M}^{-1}$ ; (8) it binds to ErbB2 with a dissociation constant of 500 nM or less; (9) it binds to ErbB2 with a dissociation constant of 10 nM or less; (10) it binds to ErbB2 with a dissociation constant of 150 pM or less; (11) it binds to ErbB2 with a dissociation constant of 60 pM or less.

## III. Nucleic Acids, Cloning and Expression Systems

**[0125]** In another aspect, the invention provides isolated nucleic acids encoding an anti-ErbB2 binding protein of the invention. The nucleic acids may comprise DNA or RNA, and they may be synthetic (completely or partially) or recombinant (completely or partially). Reference to a nucleotide sequence as set out herein encompasses a DNA molecule with the specified sequence, and encompasses a RNA molecule with the specified sequence in which U is substituted for T.

**[0126]** The invention also contemplates nucleic acids that comprise a coding sequence for a CDR1, CDR2 or CDR3, a frame-work sequence (including FR1, FR2, FR3 and/or FR4), a  $V_H$  domain, a  $V_L$  domain, or combinations thereof, as disclosed herein, or a sequence substantially identical thereto (e.g., a sequence at least 85%, 90%, 95%, 96%, 97%, 98%,

99% or higher identical thereto, or that is capable of hybridizing under stringent conditions to the sequences disclosed). [0127] In one embodiment, the isolated nucleic acid has a nucleotide sequence encoding a heavy chain variable region and/or a light chain variable region of an anti-ErbB2 binding protein comprising at least one heavy chain CDR or light chain CDR, respectively, chosen from the CDR amino acid sequences found in SEQ ID Nos:1-62, or a sequence encoding a CDR that differs by one or two amino acids from the CDR sequences set forth herein. In some embodiments, the nucleic acid encodes an anti-ErbB2 binding protein comprising one, two, or all 3 heavy chain CDRs, one, two or all 3 light chain CDRs or all 6 CDRS in any of an specifically exemplified antibody.

**[0128]** The nucleic acid can encode only the light chain or the heavy chain variable region, or can also encode an antibody light or heavy chain constant region, operatively linked to the corresponding variable region. In one embodiment, the light chain variable region is linked to a constant region chosen from a kappa or a lambda constant region. The light chain constant region may also be a human kappa or lambda type. In another embodiment, the heavy chain variable region is linked to a heavy chain constant region of an antibody isotype chosen from IgG (e.g., IgG₁, IgG₂, IgG₃, IgG₄), IgM, IgA₁, IgA₂, IgD, and IgE. The heavy chain constant region may be an IgG (e.g., an IgG₁) isotype.

**[0129]** The nucleic acid compositions of the present invention, while often in the native sequence (of cDNA or genomic DNA or mixtures thereof) except for modified restriction sites and the like, may be mutated in accordance with standard techniques to provide gene sequences. For coding sequences, these mutations, may affect amino acid sequence as desired. In particular, nucleotide sequences substantially identical to or derived from native V, D, J, constant, switches and other such sequences described herein are contemplated (where "derived" indicates that a sequence is identical or modified from another sequence).

**[0130]** In one embodiment, the nucleic acid differs (e.g., differs by substitution, insertion, or deletion) from that of the sequences provided (e.g., as follows: by at least one but less than 10, 20, 30, or 40 nucleotides; at least one but less than 1%, 5%, 10% or 20% of the nucleotides in the subject nucleic acid). Also within the invention are ErbB2 binding proteins encoded by a nucleic acid that hybridizes under stringent conditions to a nucleic acid specifically exemplified herein or to its complement. If necessary for this analysis the sequences should be aligned for maximum homology. "Looped out" sequences from deletions or insertions, or mismatches, are considered differences. The difference may be at a nucleotide (s) encoding a non-essential residue(s), or the difference may be a conservative substitution(s).

**[0131]** The invention also provides nucleic acid constructs in the form of plasmids, vectors, transcription or expression cassettes, that comprise at least one nucleic acid as described herein as well as a host cell that comprises at least one nucleic acid described herein. Suitable host cells for the expression of a binding protein of the invention well be well known in the art and include mammalian, plant, insects, bacterial or yeast cells.

**[0132]** Also provided are the methods of making an anti-ErbB2 antibody of the invention that is encoded by the nucleic acid(s) comprising sequence described herein. The method comprises culturing host cells under appropriate conditions to express the protein from the nucleic acid. Following expression and production, the encoded pp may be isolated and/or purified using any suitable technique, then used as appropriate. The method can also include the steps of fusing a nucleic acid encoding a scFv with nucleic acids encoding a Fc portion of an antibody and expressing the fused nucleic acid in a cell. The method can also include a step of germ lining.

**[0133]** Antigen-binding fragments,  $V_H$  and/or  $V_L$  domains, and encoding nucleic acid molecules and vectors may be isolated and/or purified from their natural environment, in substantially pure or homogenous form, or, in the case of nucleic acid, free or substantially free of nucleic acid or genes of origin other than the sequence encoding a polypeptide with the require function.

**[0134]** Systems for cloning and expressing polypeptides in a variety of host cells are known in the art. Cells suitable for producing antibodies are described in, for example, Fernandez et al. (1999) Gene Expression Systems, Academic Press, eds. In brief, suitable host cells include mammalian cells, insect cells, plant cells, yeast cells, or prokaryotic cells, e.g., *E. coli*. Mammalian cells available in the art for heterologous polypeptide expression include lymphocytic cell lines (e.g., NSD), HEK293 cells, Chinese hamster ovary (CHO) cells, COS cells, HeLa cells, baby hamster kidney cells, oocyte cells, and cells from a transgenic animal, e.g., mammary epithelial cell.

[0135] In one embodiment, all or a portion of an anti-ErbB2 antibody selected from S1R2A_CS_1F7, S1R2A_CS_ 1D11, S1R2C_CS_1D3, S1R2C_CS_1H12, S1R2A_CS_ 1D3, S1R3B2_BMV_1 µl, S1R3C1_CS_1D3, S1R3B2_ DP47_1E8, S1R3B2_BMV_1G2, S1R3B2_BMV_1H5, S1R3C1_CS_1A6, S1R3B2_DP47_1C9, S1R3B2_DP47_ 1E10, S1R3C1_CS_1B10, S1R3A1_BMV_1F3, S1R3B1_ BMV_1G11, S1R3A1_BMV_1G4, S1R3B1_BMV_ 1H11, S1R3A1_CS_1B9, S1R3B1_BMV_1H9, S1R3A1_ CS_1B10, S1R3B1_BMV_1C12, S1R3C1_BMV_1H11 or S1R3B1_BMV_1A1 is expressed in HEK293 or CHO cells. In other embodiments, one or more nucleic acids encoding an anti-ErbB2 binding protein of the invention are placed under the control of a tissue-specific promoter (e.g., a mammary specific promoter) and the antibodies are produced in transgenic animals. For example, the antibodies are secreted into the milk of the transgenic animal, such as a transgenic cow, pig, horse, sheep, goat or rodent.

**[0136]** Suitable vectors may be chosen or constructed to contain appropriate regulatory sequences, including promoter sequences, terminator sequences, polyadenylation sequences, enhancer sequences, marker genes, and other sequences. The vectors may also contain a plasmid or viral backbone. For details, see Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press (1989). Many established techniques used with vectors, including the manipulation, preparation, mutagenesis, sequencing, and transfection of DNA, are described in Current Protocols in Molecular Biology, Second Edition, Ausubel et al. eds., John Wiley & Sons (1992).

**[0137]** A nucleic acid encoding all or part of an anti-ErbB2 binding protein of the invention may be introduced into a host cell by any readily available means. For eukaryotic cells, suitable transfection techniques may include calcium phosphate, DEAE-Dextran, electroporation, liposome-mediated transfection, and transduction using retrovirus or other viruses, e.g., vaccinia or baculovirus. For bacterial cells, suitable techniques may include calcium chloride transformation, electroporation, and transfection using bacteriophage.

DNA introduction may be followed by a selection method (e.g., drug resistance) to select cells that contain the nucleic acid.

# IV. Therapeutic Uses of Anti-ErbB2 Binding Proteins

**[0138]** Anti-ErbB2 binding proteins of the invention may be ErbB2 agonists or antagonists. An agonist ErbB2 binder of the invention increases HER2 tyrosine phosphorylation in the absence or presence of other HER2 agonists such as Heregulin or Epidermal Growth Factor (EGF). Certain HER2 agonists of the invention increase phosphorylation of HER2 pathway proteins. In some embodiments, the agonist of the invention increase phosphorylation of AKT, MAPK and/or ERK. In some embodiments, the HER2 agonist of the invention decreases proliferation and/or increases cell death of a cancer cell, in vitro and in vivo.

**[0139]** Anti-ErbB2 binding proteins that act as antagonists to ErbB2 can be used to reduce at least one ErbB2-mediated activity, such as reducing ErbB2-mediated tyrosine phosphorylation, decreased heterodimerization of ErbB2 with other ERBB-family members, decreased ErbB2-mediated cell signalling and decreased growth or proliferation of ErbB2-expressing cells. In one embodiment, anti-ErbB2 binding proteins of the invention are used in a method for decreasing tumor growth, the method comprising contacting an ErbB2 expressing cell with a binding protein of the invention to modulate cell proliferation, cytolytic activity, cytokine secretion, or chemokine secretion.

**[0140]** Accordingly, the binding proteins of the invention can be used to directly or indirectly inhibit or reduce the activity (e.g., proliferation, differentiation, and/or survival) of cells expressing ErbB2, and, thus, can be used to treat a variety of disorders including hyperproliferative disorders.

[0141] The binding proteins of the invention can be used to treat hyperproliferative disorders associated with activity of ErbB2 by administering the antibodies in an amount sufficient to inhibit or reduce hyperproliferation and/or to increase cell death, such as by apoplosis of ErbB2 expressing cells in a subject and allowing the antibodies to treat or prevent the disorder. ErbB2 is expressed in a number of cancers including, but not limited to, breast, bladder, cervical, ovarian, prostate, testicular, oral, colorectal, lung and pancreatic, cancers and in childhood medulloblastoma, oral squamous cell carcinoma, gastric cancer cholangio carcinoma, osteosarcoma, primary Fallopian tube carcinoma, salivary gland tumors and synovial sarcoma. Binding proteins of the invention may be used to inhibit the progression of neoplasms, e.g. squamous cell carcinomas, basal cell carcinomas, transitional cell papillomas and carcinomas, adenomas, adenocarcinoma. According to the invention, an anti-ErbB2 binding protein of the invention can be administered to a subject in need thereof as part of a regimen that comprises another therapeutic modality, such as surgery or radiation.

# V. Combination Therapy

**[0142]** According to the invention, a composition suitable for pharmaceutical use comprising at least one anti-ErbB2 binding protein further comprises at least one additional therapeutic agent. The therapy is useful for treating ErbB2-mediated pathological conditions or disorders including cancer. The term "in combination" in this context means that the binding protein composition and the additional therapeutic

agent are given as part of a treatment regimen. In some embodiments, the anti-ErbB2 binding protein is administered substantially contemporaneously, either simultaneously or sequentially. In some embodiments, in which administration is sequential, at the onset of administration of the second agent, the first of the two agents is still detectable at effective concentrations at the site of treatment. In another embodiment, if given sequentially, at the onset of administration of the second compound, the first of the two compounds is not detectable at effective concentrations at the site of treatment. [0143] For example, the combination therapy can include at least one anti-ErbB2 binding protein of the invention coformulated with, co-administered with, or administered as part of the same therapeutic regimen as at least one additional therapeutic agent. The additional agents may include at least but is not limited to mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, antiproliferative agents, kinase inhibitors, angiogenesis inhibitors, growth factor inhibitors, cox-I inhibitors, cox-II inhibitors, radiation, cell cycle inhibitors, enzymes, antihormones, statins, and anti-androgens.

**[0144]** In other embodiments, at least one anti-ErbB2 binding protein can be co-formulated with, and/or co-administered with, at least one anti-inflammatory drug, immunosuppressant, metabolic inhibitor, and enzymatic inhibitor.

**[0145]** In other embodiments, an anti-ErbB2 antibody can be used in combination with at least one binding protein, such as an antibody, directed at other cancer targets. Another aspect of the present invention accordingly relates to kits for carrying out the administration of the anti-ErbB2 binding protein alone or in combination with other therapeutic agents. In one embodiment, the kit comprises at least one anti-ErbB2 binding protein formulated in a pharmaceutical carrier, and at least one additional therapeutic agent, formulated as appropriate in one or more separate pharmaceutical preparations.

**[0146]** In one embodiment, the present inventive binding proteins can be administered in combination with (e.g., prior to, concurrently with, or subsequent to) one or more other therapeutic agents. Such therapeutic agents include, for example, cytotoxic agents that inhibit or prevent the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (e.g. I131, I125, Y90 and Re186), chemotherapeutic agents, growth inhibitory agents, cytokine, and toxins such as enzymatically active toxins of bacterial, fungal, plant or animal origin, or fragments thereof.

[0147] Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (CY-TOXAN™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK®; razoxane; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (TAXOTERE®, Rhône-Poulenc Rorer, Antony, France); chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylomithine (DMFO); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[0148] A growth inhibitory agent when used herein refers to a compound or composition that inhibits growth of a cell, especially an ErbB2-overexpressing cancer cell either in vitro or in vivo. In the context of the present invention, the growth inhibitory agent can be one that significantly reduces the percentage of ErbB2 overexpressing cells in S phase and the binding proteins of the present invention may potentially sensitize the cells to such an S phase agent. S-phase blockers include the vincas (vincristine and vinblastine), taxol, and topo II inhibitors such as doxorubicin, daunorubicin, etoposide, and bleomycin. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), include agents that induce G1 arrest and M-phase arrest. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in The Molecular Basis of Cancer, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogens, and antineoplastic drugs" by Murakami et al. (WB Saunders: Philadelphia, 1995), especially p. 13.

[0149] Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor, fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor- $\alpha$  and - $\beta$ ; mullerianinhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF- $\beta$ ; platelet-growth factor; transforming growth factors (TGFs) such as TGF- $\alpha$  and TGF- $\beta$ ; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon- $\alpha$ , - $\beta$ , and - $\gamma$ ; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1a, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12; a tumor necrosis factor such as TNF- $\alpha$  or TNF- $\beta$ ; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines.

**[0150]** The invention also pertains to immunoconjugates comprising the binding proteins described herein conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g. an enzymatically active toxin of bacterial, fungal, plant or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

**[0151]** Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof which can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin and the tricothecenes. A variety of radio-nuclides are available for the production of radioconjugated anti-ErbB2 binding proteins. Examples include 212Bi, 131I, 131In, 90Y and 186Re.

**[0152]** Immunoconjugates comprising a member of the potent family of antibacterial and antitumor agents, known collectively as the calicheamicins or the LL-E33288 complex, (see U.S. Pat. No. 4,970,198 (1990)) are also contemplated. The most potent of the calicheamicins is designated  $\gamma$ 1, which is herein referenced simply as gamma. These compounds contain a methyltrisulfide that can be reacted with appropriate thiols to form disulfides, at the same time introducing a functional group such as a hydrazide or other functional group that is useful in attaching a calicheamicin derivative to a carrier. (See U.S. Pat. No. 5,053,394). Conjugation methods for preparing monomeric calicheamicin derivative/

carrier have been disclosed (see U.S. Pat. No. 5,712,374 and U.S. Pat. No. 5,714,586, incorporated herein in their entirety).

[0153] Conjugates of the binding protein and cytotoxic agent can be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl)hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al. Science 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the binding protein.

**[0154]** Effective amounts of the other therapeutic agents are well known to those skilled in the art. However, it is well within the skilled artisan's purview to determine the other therapeutic agent's optimal effective amount range. The binding proteins of the present invention and the other therapeutic agent(s) can act additively or, alternatively, synergistically. In one embodiment of the invention, where another therapeutic agent(s) is administered to an animal, either the effective amount of the binding protein of the present invention or the other therapeutic agent(s) can be administered in an amount that is less than its effective amount would be where the other therapeutic agent is not administered. In this case, without being bound by theory, it is believed that the two (or more) act synergistically.

# VI. Diagnostic Uses

**[0155]** In a further aspect, a binding protein of the invention may also be used to detect the presence of ErbB2 or ErbB2 expressing cells in a biological sample. By correlating the presence or level of ErbB2 with a medical condition, one of skill in the art can diagnose the associated medical condition, including cancer.

**[0156]** Binding protein-based, including antibody-based detection methods are well known in the art, and include ELISA, radioimmunoassays, immunoblots, Western blots, flow cytometry, immunofluorescence, immunoprecipitation, and other related techniques. The antibodies may be provided in a diagnostic kit that incorporates at least one of these procedures to detect ErbB2. The kit may contain other components, packaging, instructions, or other material to aid the detection of the protein and use of the kit.

**[0157]** Binding proteins of the invention may be modified with detectable markers, including ligand groups (e.g., biotin), fluorophores and chromophores, radioisotopes, electron-dense reagents, or enzymes. Enzymes are detected by their activity. For example, horseradish peroxidase is detected by its ability to convert tetramethylbenzidine (TMB) to a blue pigment, quantifiable with a spectrophotometer. Other suitable binding partners include biotin and avidin, IgG and protein A, and other receptor-ligand pairs known in the art.

**[0158]** Binding proteins of the invention can also be functionally linked (e.g., by chemical coupling, genetic fusion, non-covalent association or otherwise) to at least one other molecular entity, such as another antibody (e.g., a bispecific or a multispecific antibody), toxins, radioisotopes, cytotoxic or cytostatic agents, among others for therapeutic use. Other permutations and possibilities are apparent to those of ordinary skill in the art, and they are considered equivalents within the scope of this invention.

**[0159]** Further, the anti-ERRB2 binding proteins can be used to detect the presence, isolate, and/or to quantitate ErbB2-expressing cells in a sample from a subject or by in vivo imaging.

# VII. Pharmaceutical Compositions and Methods of Administration

[0160] In still another aspect, the invention provides compositions comprising an anti-ErbB2 binding protein of the invention. The compositions may be suitable for pharmaceutical use and administration to patients. The compositions comprise a binding protein of the present invention and a pharmaceutically acceptable carrier. The composition may optionally comprise a pharmaceutical excipient. As used herein, "pharmaceutical excipient" includes solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, etc., that are compatible with pharmaceutical administration. Use of these agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions. The pharmaceutical compositions may also be included in a container, pack, or dispenser together with instructions for administration.

**[0161]** A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Methods to accomplish the administration are known to those of ordinary skill in the art. Pharmaceutical compositions may be topically or orally administered, or capable of transmission across mucous membranes. Examples of administration of a pharmaceutical composition include oral ingestion or inhalation. Administration may also be intravenous, intraperitoneal, intramuscular, intracavity, subcutaneous, cutaneous, or transdermal.

**[0162]** Solutions or suspensions used for intradermal or subcutaneous application typically include at least one of the following components: a sterile diluent such as water, saline solution, fixed oils, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetate, citrate, or phosphate; and tonicity agents such as sodium chloride or dextrose. The pH can be adjusted with acids or bases. Such preparations may be enclosed in ampoules, disposable syringes, or multiple dose vials.

**[0163]** Solutions or suspensions used for intravenous administration include a carrier such as physiological saline, bacteriostatic water, Cremophor  $EL^{TM}$  (BASF, Parsippany, N.J.), ethanol, or polyol. In all cases, the composition must be sterile and fluid for easy syringability. Proper fluidity can often be obtained using lecithin or surfactants. The composition must also be stable under the conditions of manufacture and storage. Prevention of microorganisms can be achieved with antibacterial and antifungal agents, e.g., parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, etc. In many cases, isotonic agents (sugar), polyalcohols (mannitol and sorbitol), or sodium chloride may be included in the composition. Prolonged absorption of the composition can be

accomplished by adding an agent that delays absorption, e.g., aluminum monostearate and gelatin.

**[0164]** Oral compositions include an inert diluent or edible carrier. The composition can be enclosed in gelatin or compressed into tablets. For the purpose of oral administration, the antibodies can be incorporated with excipients and placed in tablets, troches, or capsules. Pharmaceutically compatible binding agents or adjuvant materials can be included in the composition. The tablets, troches, and capsules, may contain (1) a binder such as microcrystalline cellulose, gum tragacanth or gelatin; (2) an excipient such as starch or lactose, (3) a disintegrating agent such as alginic acid, Primogel, or corn starch; (4) a lubricant such as magnesium stearate; (5) a glidant such as colloidal silicon dioxide; or (6) a sweetening agent or a flavoring agent.

**[0165]** The composition may also be administered by a transmucosal or transdermal route. For example, antibodies that comprise a Fc portion may be capable of crossing mucous membranes in the intestine, mouth, or lungs (via Fc receptors). Transmucosal administration can be accomplished through the use of lozenges, nasal sprays, inhalers, or suppositories. Transdermal administration can also be accomplished through the use of a composition containing ointments, salves, gels, or creams known in the art. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used. For administration by inhalation, the antibodies are delivered in an aerosol spray from a pressured container or dispenser, that contains a propellant (e.g., liquid or gas) or a nebulizer.

**[0166]** In certain embodiments, the binding proteins of this invention are prepared with carriers to protect against rapid elimination from the body. Biodegradable polymers (e.g., ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid) are often used. Methods for the preparation of such formulations are known by those skilled in the art. Liposomal suspensions can be used as pharmaceutically acceptable carriers too. The liposomes can be prepared according to established methods known in the art (U.S. Pat. No. 4,522,811).

**[0167]** The binding proteins or compositions of the invention are administered in therapeutically effective amounts as described. Therapeutically effective amounts may vary with the subject's age, condition, sex, and severity of medical condition. Appropriate dosage may be determined by a physician based on clinical indications. The binding proteins or compositions may be given as a bolus dose to maximize the circulating levels of protein for the greatest length of time. Continuous infusion may also be used after the bolus dose.

**[0168]** As used herein, the term "subject" is intended to include human and non-human animals. Subjects may include a human patient having a disorder characterized by cells that express ErbB2, e.g., a cancer cell or an immune cell. The term "non-human animals" of the invention includes all vertebrates, such as non-human primates, sheep, dogs, cows, chickens, amphibians, reptiles, etc.

**[0169]** Examples of dosage ranges that can be administered to a subject can be chosen from: 1 µg/kg to 20 mg/kg, 1 µg/kg to 10 mg/kg, 1 µg/kg to 1 mg/kg, 10 µg/kg to 1 mg/kg, 10 µg/kg to 1 mg/kg, 250 µg/kg to 2 mg/kg, 250 µg/kg to 1 mg/kg, 500 µg/kg to 2 mg/kg, 500 µg/kg to 1 mg/kg, 1 mg/kg, 500 µg/kg to 5 mg/kg, 5 mg/kg to 10 mg/kg, 10 mg/kg to 20 mg/kg, 15 mg/kg to 20 mg/kg, 10 mg/kg to 25 mg/kg, 20 mg/kg to 25 mg/kg, and 20 mg/kg to 30 mg/kg (or higher).

These dosages may be administered daily, weekly, biweekly, monthly, or less frequently, for example, biannually, depending on dosage, method of administration, disorder or symptom(s) to be treated, and individual subject characteristics. Dosages can also be administered via continuous infusion (such as through a pump). The administered dose may also depend on the route of administration. For example, subcutaneous administration may require a higher dosage than intravenous administration.

**[0170]** In certain circumstances it may be advantageous to formulate compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited for the patient. Each dosage unit contains a predetermined quantity of antibody calculated to produce a therapeutic effect in association with the carrier. The dosage unit depends on the characteristics of the antibodies and the particular therapeutic effect to be achieved.

**[0171]** Toxicity and therapeutic efficacy of the composition can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., determining the  $LD_{50}$  (the dose lethal to 50% of the population) and the  $ED_{50}$  (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio  $LD_{50}$ /  $ED_{50}$ . Binding proteins that exhibit large therapeutic indices may be less toxic and/or more therapeutically effective.

[0172] The data obtained from the cell culture assays and animal studies can be used to formulate a dosage range in humans. The dosage of these compounds may lie within the range of circulating antibody concentrations in the blood, that includes an  $ED_{50}$  with little or no toxicity. The dosage may vary within this range depending upon the dosage composition form employed and the route of administration. For any antibody used in the present invention, the therapeutically effective dose can be estimated initially using cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the  $IC_{50}$  (i.e., the concentration of antibody that achieves a half-maximal inhibition of symptoms). The effects of any particular dosage can be monitored by a suitable bioassay. Examples of suitable bioassays include DNA replication assays, transcription-based assays and ErbB2 binding assavs.

## EXAMPLES

#### Example 1

#### Selection of Anti-ErbB2 scFv's

**[0173]** Single chain fragment variable (scFv) moieties that bind to the extracellular domain (ECD) of Her2 (ErbB2) were identified following three rounds of selection using three phagemid libraries: the Bone Marrow Vaughan (BMV) library (Vaughan et al, 1996), the combined spleen (CS) library and the DP47 library (unpublished). Several Her2-Fc proteins or cell lines expressing various forms of Her2 were used during the selection and subsequent screening steps (see Table 3). The selection strategies are outlined in FIG. 1.

[0174] Selection Using Biotinylated HER2 Proteins

**[0175]** For selections involving biotinylated protein, aliquots of phage and magnetic streptavidin beads (Dynabeads M-280 streptavidin) were blocked separately in 3% milk/PBS for 1 hour at room temperature in a rotary mixer (20 rpm). Each selection was preceded by a de-selection step. For deselection, blocked phage were incubated with the pre-blocked magnetic beads and incubated for one hour on a rotary shaker (20 rpm). The de-selected library was collected by pelleting the beads using a magnetic separator. A 1  $\mu$ M concentration of a non-biotinylated competitor protein (eg, irrelevant MIgG2a protein) was added to the de-selected phage and incubated for a further hour.

**[0176]** Biotinylated selection antigen (at various concentrations as indicated in FIG. 1) was incubated with the deselected phage library for 2 hours at room temp on a rotary mixer (20 rpm) followed by a 15 minute incubation with pre-blocked magnetic beads. Beads were separated using a magnetic separator and washed 10 times with PBS/0.1% Tween 20 and 3 times with PBS. Bound phage were eluted by incubation with a 10 ug/ml solution of trypsin in PBS for 30 minutes at 37° C. (100 rpm) followed by separation from the magnetic beads.

[0177] Selection Using Cells Expressing HER2ECD or ECD Fragments

**[0178]** For selections involving cells, approximately  $4 \times 10^7$  de-selection cells (ie. cells not expressing the antigen of interest) and  $2 \times 10^7$  capture (i.e., selection) cells (cells expressing the antigen of interest) were collected using PBS/5 mM EDTA and washed twice with PBS. Cells were blocked with 3% milk/1% BSA/PBS for 1 hour at 4° C. on a rotary mixer (20 rpm). De-selection cells were collected by centrifugation, re-suspended in blocked phage and incubated at 4° C. as before. Both the capture and de-selection cells were pelleted and the capture cells were resuspended with the de-selected phage supernatant and incubated at 4° C. as before. The

capture cells were washed three times with cold PBS/0.1% Tween 20 and three times with cold PBS. Phage were eluted by re-suspending the cells in a 10 µg/ml trypsin solution and incubated for 30 min at 37° C. (100 rpm). Eluted phage were harvested in the supernatant following centrifugation of cells. Eluted phage were used to infect 10 ml of an E. coliTG1 culture that had been grown to mid-logarithmic phase (corresponding to an  $OD_{600}$  of ~0.5). Bacteria were infected with phage for 1 hour at 37° C. with shaking at 150 rpm, concentrated following a centrifugation step and plated on 2×TY agar bioassay plates containing 2% glucose and 100 ug/ml ampicillin (2×TYAG). Various dilutions of E. coli culture infected with either input or output phage were also plated on 2×TYAG agar to determine phage titers. Following overnight growth at 30° C., 10 ml of 2×TYAG medium was added to each bioassay plate and the cells were re-suspended by scraping the bacterial lawn. Glycerol was added to this cell suspension to give a final concentration of 17% and stored in aliquots at -80° C. until further use. To rescue phage for the next round of selection, 100 µl of this cell suspension was used to inoculate 20 ml 2×TYAG medium, that was grown at  $37^\circ$  C. (300 rpm) to an OD_{600} of 0.3-0.5. Cells were then super-infected with 3.3  $\mu l$  of MK13K07 helper phage and incubated at 37° C. (150 rpm) for 1 hour. The cells were then centrifuged and the pellet re-suspended in a kanamycin/nonglucose containing medium (2×TY with 50 µg/ml kanamycin and 100 ug/ml ampicillin). This culture was grown overnight at 30° C. (300 rpm). Phage were harvested in the supernatant following centrifugation and were ready to use in the second and third rounds of selection as described in FIG. 1.

TABLE 3

Jame Descripti	Sequence for Her2 region of fusion protein
(Synonyms: domain (E	extracellularMELAALCRWGLLLALLPPGAASTQVof Her2CTGTDMKLRLPASPETHLDMLRHLYlth a mIgG2aQGCQVVQGNLELTYLPTNASLSFLQDIQEVQGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTEILKGGVLIQRNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTDCCHEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCPLHNQEVTAEDGTQRCEKCSKPCARVCYGLGMEHLREVRAVTSANIQEPAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQLQVFETLEEITGYLYISAWPDSLPDLSVFQNLQVIRGRILHNGAYSLTLQGLGISWLGLRSLRELGSGLALIHNNTHLCFVHTVPWDQLFRNPHQALLHTANRPEDECVGEGLACHQLCARGHCWGPGPTQCVNCSQFLRQQECVEECRVLQGLPREYVNARHCLPCHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVDLKFPDEEGACQPCPINCTHSCVDL

TABLE 3-continued

Name	Description	Sequence for Her2 region of fusion protein
Her017P (Synonyms: EQR; HER017)	Her2 ECD with a deletion in the membrane proximal 9 amino acids expressed with a mIgG2a Fc tail	MELAALCRWGLLLALLPPGAASTQV CTGTDMKLRLPASPETHLDMLRHLY QGCQVVQGNLELTYLPTNASLSFLQ DIQEYQGYVLIAHNQVRQVPLQRLR IVRGTQLFEDNYALAVLDNGDPLNN TTPVTGASPGGLRELQLRSLTEILK GGVLIQRNPQLCYQDTILWKDIFHK NNQLALTLIDTMRSRACHPCSPMCK GSRCWGESSEDCQSLTRTVCAGG CARCKGPLPTDCCHEQCAAGCTGP KHSDCLACLHFNHSGICELHCPALV TYNTDTFESMPNPGRYTFGASCV TACPYNYLSTDVGSCTLVCPLHNQE VTAEDGTQRCEKCSKPCARVCYGL GMEHLREVRAVTSANIQEFAGCKKI FGSLAFLPESFDGDPASNTAPLQPE QLQVFETLEEITGYLYISAWPDSLPD LSVFQNLQVIRGRILHNGAYSLTLQ GLGISWLGLRSLRELGSGLALIHHN THLCFVHTVPWDQLFRNPHQALLH TANRPEDECVGEGLACHQLCARGH CWGPGPTQCVNCSQFLRGQECVE ECRVLQGLPREYVNARHCLPCHPE CQPQNGSVTCFGFEADQCVACH YKDPPFCVARCPSGVKPDLSVPI WKFPDEEGACQPCPINCTHSCVDL DDKGCPAEQR (SEQ ID NO: 243)
Her018P (Synonyms: 1.8; HER018)	Her2 ECD with a deletion in the CR2 (Domain IV) region expressed with a mIgG2a Fc tail	MELAALCRWGLLLALLPPGAASTQV CTGTDMKLRLPASPETHLDMLRHLY QGCQVVQGNLELTYLPTNASLSFLQ DIQEYQGYVLIAHNQVRQVPLQRLR IVRGTQLFEDNYALAVLDNGDPLNN TTPVTGASPGGLRELQLRSLTEILK GGVLIQRNPQLCYQDTILWKDIFHK NNQLALTLIDTNRSRACHPCSPMCK GSRCWGESSEDCQSLTRTVCAGG CARCKGPLPTDCCHEQCAAGCTGP KHSDCLACLHFNHSGICELHCPALV TYNTDTFESMPNPEGRYTFGASCV TACPYNYLSTDVGSCTLVCPLHNQE VTAEDGTQRCEKCSKPCARVCYGL GMEHLREVRAVTSANIQEFAGCKKI FGSLAFLPESFDGDPASNTAPLQPE QLQVFETLEEITGYLYISAWPDSLPD LSVFQNLQVIRGRILHNGAYSLTLQ GLGISWLGLRSLRELGSGLALIHNN THLCFVHTVPWDQLFRNPHQALLH TANRPEDECVGGGLACHQLCARGH CWGPGPTQCVNCSQFLRGQECVE ECRVLQGLPREYVNARHCLPCHPE CQPQNGSVTCFGFEADQCVACH YKDPPFCVAR (SEQ ID NO: 244)
Her054P (Synonyms: L1-CR1; 1.0)	Domains I (L1) and II (CR-1) of Her2 expressed with a mIgG2a Fc tail	MELAALCRWGLLLALLPPGAASTQV CTGTDMKLRLPASPETHLDMLRHLY QGCQVVQGNLELTYLPTNASLSFLQ DIQEVQGYVLIAHNQVRQVPLQRLR IVRGTQLFEDNYALAVLDNGDPLNN TTPVTGASPGGLRELQLRSLTEILK GGVLIQRNPQLCYQDTILWKDIFHK NNQLALTLIDTNRSRACHPCSPMCK GSRCWGESSEDCQSLTRTVCAGG CARCKGPLPTDCCHEQCAAGCTGP KHSDCLACLHFNHSGICELHCPALV TYNTDTFESMPNPEGRYTFGASCV TACPYNYLSTDVGSCTLVCPLHNQE VTAEDGTQRCEKCSKPC (SEQ ID NO: 245)

Name	Description	Sequence for Her2 region of fusion protein
	length	Protein MELAALCRWGLLLALLPPGAASTQV CTGTDMKLRLPASPETHLDMLRHLY QGCQVVQGNLELTYLPTNASLSFLQ DIQEVQGYULIANNQVRQVPLQRLR IVRGTQLFEDNYALAVLDNGDPLNN TTPVTGASPGGLRELQLRSLTEILK GGVLIQRNPQLCYQDTILWKDIFHK NNQLALTLIDTNRSRACHPCSPMCK GSRCWGESSEDCQSLTRTVCAGG CARCKGPLPTDCCHEQCAAGCTGP KHSDCLACLHFNHSGICELHCPALV TYNTDTFESMPNEGRYTFGASCV TACPYNYLSTDVGSCTLVCPLHNQE VTAEDGTQRCEKCSKPCARVCYGL GMEHLREVRAVTSANIQEFAGCKKI FGSLAFLPESFDGDPASNTAPLQPE QLQVFETLEEITGYLYISAWPDSLPD LSVPQNLQVIRGRILHNGAYSLTLQ GLGISWLGLRSLRELGSGLALIHHN THLCFVHTVPWQLFRNPHQALLH TANRPEDECVGEGLACHQLCARGH CWGPGPTQCVNCSQFLRGQECVE ECRVLQGLPREYVNARHCLPCHPE CQPQNGSVTCFGPEADQCVACAH YKDPPFCVARCPSGVKPDLSYMPI WKFPDEEGACQPCPINCTHSCVDL DDKGCPAEQRASPLTSIISAVVGILL VVVLGVVFGILIKRRQQKIRKYTMRR LLQETELVEPLTPSGAMPNQAQMRI LKETELRKVKVLGSGAFGTVYKGIW IPDGENVKIPVAIKVLRENTSPKANK EILDEAYVMAGVGSPYVSRLLGICLT STVQLVTQLMPYGCLLDHVRENRG RLGSQDLNWCMQIAKGMSYLEDV ALESILRRFTHQSDVWSYGVTW ELMTFGARPYDGIPAREIPDLLEKGE RLPQPPICTIDVMIMVKCMMIDSE CRPRFRELVSEFSMARDPQRFVVI QHEDLGPASPLDSTYRSLLEDDD MGDLVDAEEYLVPQQGFFCPDPAP GAGGMVHRHRRSSTRSGGDLT LGLEPSEEAPRSPLAPSEGAGSDV FDGDLGMGAAKGLQSLPTHDPSPL QRYSEDPTVPLPSETDGYVAPLTCS
		PQPEYVNQPDVRPQPPSPEEGPLP AARPAGATLERPKTLSPGKNGVVK DVFAFGGAVENPEYLTPQGGAAPQ PHPPPAFSPAFDNLYYWDQDPPER GAPPSTFKGTPTAENPEYLGLDVPV (SEQ ID NO: 246)

TABLE 3-continued

#### Example 2

# Preparation of Phage or Crude Periplasmic Material for Use in ELISAs

**[0179]** ScFvs can be expressed either on the surface of a phage particle or in solution in the bacterial periplasmic space, depending upon the growth conditions used. To induce release of scFv into the periplasm, 96-deepwell plates containing  $2\times$ TY media with 0.1% glucose/100 µg/ml ampicillin were inoculated from thawed glycerol stocks (one clone per well) using the QPix2 Colony picker (Genetix) and grown at 37° C. (999 rpm) for ~4 hours. Cultures were induced with IPTG at a final concentration of 0.02 mM and grown overnight at 30° C. (999 rpm). The contents of the bacterial periplasm (peripreps) were released by osmotic shock. Briefly,

plates were centrifuged and pellets were resuspended in 150  $\mu$ l HEPES periplasmic buffer (50 mM HEPES, pH7.4/0.5 mM EDTA/20% Sucrose), followed by the addition of 150  $\mu$ l 1:5 HEPES:water and incubated on ice for 30 minutes. Plates were centrifuged and the scFv-containing supernatant was harvested.

**[0180]** To prepare phage expressing scFv on their surface, 96-well plates containing 150  $\mu$ l 2×TY media with 2% glucose/100  $\mu$ g/ml ampicillin were inoculated from thawed glycerol stocks as described above and grown at 37° C. (700 rpm) for ~4 hours. 20  $\mu$ l of a 1:1000 dilution of helper phage (~2×10⁸ pfu) was added and the plates incubated for a further hour at 37° C. (300 rpm). Plates were centrifuged and the media was replaced with a kanamycin/non-glucose containing media (2×TY with 50  $\mu$ g/ml kanamycin and 100 ug/ml ampicillin). Plates were grown overnight at  $30^{\circ}$  C. (700 rpm) and phage were harvested in the supernatant following centrifugation.

**[0181]** Thirty-one Her2-binding ScFv's were identified by three rounds of screenings as illustrated in FIG. 1. These ScFv's specifically bind to the ECD region of Her2.

**[0182]** Among these thirty-one Her2-binding ScFv's, fourteen ScFv's were expressed on the surface of a phage particle for the purpose of screening. These ScFv's are: S1R2A_CS_ 1F7, S1R2A_CS_1D11, S1R2C_CS_1D3, S1R2C_CS_ 1H12, S1R2A_CS_1D3, S1R3B2_BMV_1E1, S1R3C1_ CS_1D3, S1R3B2_DP47_1E8, S1R3B2_BMV_1G2, S1R3B2_BMV_1H5, S1R3C1_CS_1A6, S1R3B2_ DP47_1C9, S1R3B2_DP47_1E10, and S1R3C1_CS_ 1B10 (FIGS. **2** and **3**).

## Example 3

ELISA to Test Her2 Protein Construct Binding by scFvs Expressed in the *E. coli* Periplasm, on the Surface of Phage, or in Mammalian Cells as Fc Fusions

[0184] Various Her2-Fc proteins (e.g., Her008P, Her017P, Her018P, etc.) or a negative control murine IgG2a protein were coated overnight at 4° C. on 96-well Nunc Maxisorp at a concentration of 1 ug/ml in PBS. Alternatively, pre-blocked streptavidin-coated plates (Greiner) were coated with biotinylated Her2-Fc proteins for 1 hour at room temperature at a concentration of 1 ug/ml in block buffer (3% skim milk/1% BSA/PBS). Plates were washed three times using PBS and blocked for 1 hour at room temperature in 3% skim milk/1% BSA/PBS. Phage or peripreps were prepared as described above and were blocked for 1 hour at room temperature in an equal volume of 6% skim milk/1% BSA/PBS. Blocked plates were washed five times with PBS and 50 µl/well of blocked phage or periprep were transferred to the appropriate plates and incubated for 1 hour at room temperature. A 1 ug/ml solution of HERCEPTIN® (trastuzumab) (in blocking buffer) was added to well H12 of each plate to serve as a positive control. Plates were washed five times with PBS prior to the addition of a 1:250 dilution of anti-myc peroxidase (Roche), a 1:2500 dilution of anti-M13 peroxidase (Amersham Biosciences) or a 1:5000 or 1:1000 dilution of goat anti-human peroxidase (Southern Biotech) secondary antibody to detect bound scFv, phage, HERCEPTIN® (trastuzumab) or SMIP, respectively. Plates were incubated for a further hour at room temperature and washed seven times with PBS. Signal was developed using TMB, the reaction stopped with  $\rm H_2SO_4$  and the absorbance read at 450 nm on an Envision plate reader (Perkin Elmer). The results of these binding assays are shown in FIG. 5.

**[0185]** Alternatively, plates were coated with 1 ug/ml of a SMIP (Her030, Her033/Her067, Her018) or antibody (Herceptin®), positive control). SMIPs were used to capture 3-fold serial dilution  $(9-0 \ \mu g/ml)$  of soluble protein sample as

follows: dimeric HER2 (HERB017), monomeric HER2 (HER155), or monomeric HER2 (shed ectodomain from SKBR3 supernatant). Captured soluble protein was detected using 0.1 mg/ml anti-c-Erb B2/c-Neu (Ab-5) mouse mAb (TA-1; binds ECD; Calbiochem) and detected using HRP-conjugated Goat anti-mouse IgG (Fcg Subclass 1 specific; Jackson ImmuonoResearch).

**[0186]** The results of the SMIP binding assays are shown in FIG. **6**A-C, FIG. **7**A-**7**D and FIG. **8**. In FIG. **8**, the binding of HER018, HER026-HER039 and Herceptin® (trastuzumab) to Her2 protein constructs was scored as -, +, ++ or +++, while the binding of HER071-HER087 to Her2 protein constructs was scored as a - or +.

## Example 4

# ELISA to Measure Binding of scFvs (Expressed in the Periplasm or on the Surface of Phage) to Her2-Expressed Cells

[0187]  $2 \times 10^4$  CHOK1 cells/well were seeded in a 96-well tissue culture plate on Day 1 and incubated at  $37^{\circ}$  C./5% CO₂ for 2-4 days until a confluent monolayer was observed. Cells were washed five times with PBS (+ Ca/Mg ions) and blocked for 1 hour at room temperature with 3% skim milk/1% BSA/ PBS (+ Ca/Mg ions). Phage or peripreps were prepared as described above and were blocked for 1 hour at room temperature in an equal volume of 6% skim milk/1% BSA/PBS (+ Ca/Mg ions). Blocked plates were washed five times with PBS (+ Ca/Mg ions) and 50 µl/well of blocked phage or periprep were transferred to the appropriate plates and incubated for 1 hour at room temperature. A 1 ug/ml solution of HERCEPTIN® (trastuzumab) (in blocking buffer) was added to well H12 of each plate to serve as a positive control. Plates were washed five times with PBS (+Ca/Mg ions) prior to the addition of a 1:250 dilution of anti-myc peroxidase (Roche), a 1:2500 dilution of anti-M13 peroxidase (Amersham Biosciences) or a 1:5000 dilution of goat anti-human (Southern Biotech) secondary antibody to detect bound scFv, phage or HERCEPTIN® (trastuzumab) respectively. Plates were incubated for a further hour at room temperature and washed ten times with PBS (+ Ca/Mg ions). Signal was developed using TMB, the reaction stopped with  $H_2SO_4$  and the absorbance read at 450 nm on an ENVISION plate reader (Perkin Elmer). The results of these binding assays are shown in FIG. 5.

**[0188]** Alternatively, the cell lines tested for SMIP binding included SKBR3, BT474, 22rv1, MDA-MB-175, MDA-MB-453, MDA-MB-361 (ATCC), MDA-MB-361 (JL), and Ramos (Her2⁻/CD20⁺ control). The SMIPs tested included Her067 (c.f. Her033), Her094 (c.f. Her030), and Her018, while the controls used included Herceptin® (trastuzumab), Rituxan® (anti-CD20 mAb rituximab), and CD20-SMIP.

**[0189]** Each well of a 6 well plate was seeded with  $2 \times 10^5$  cells and incubated overnight at  $37^\circ$  C./5% CO₂. Cells were then treated with antibody or SMIP (at 10 ug/ml final) (in triplicate) and incubated for another 24 or 48 hours. After incubation, the cells were pulsed with 50 uM BrdU (Sigma) for 30 minutes at  $37^\circ$  C., the media was removed, and the cells were treated with trypsin (except Ramos) and then  $3-3.5 \times 10^5$  cells per well were stained in 100 µl Staining Buffer in the presence or absence of a SMIP or antibody one of three different concentrations (ranging from 200 nM to 0.27 nM). The SMIP or antibody treatment was removed and the cells were washed three times with PBS, pH 7.2-7.4 with 0.1% TWEEN®-20 (PBS-T). A secondary antibody (5 ug/ml Alexa

Fluor 488-conjugated Goat anti-Human IgG; Molecular Probes) was then added and incubated for 1-2 hours at room temperature. The secondary antibody was removed and the cells washed again three times with PBS-T. The cells were then fixed in 1% paraformaldehyde in Staining Buffer and analyzed 1 hour to 1 day later.

**[0190]** SMIPs maintain a similar staining pattern regardless of the amount of HER2 on the cell surface and the other ErbB receptors/ligands expressed by the cell lines (relative surface staining for ErbB1, Her2, Erb3 and production of ligand by cell lines is not shown). The SMIP/antibody staining pattern was Herceptin®>Her018>HER067 (Her033)>HER094 (Her030). The results of these binding assays are shown in FIG. 8 and FIG. 9A-9H. (In FIG. 9E, 0.82 nM HER094 data not collected due to mechanical error.)

#### Example 5

## PCR Amplification of scFv Regions for Sequencing Analysis

[0191] PCR amplification of scFvs was carried out using the KOD HOT START DNA Polymerase kit (Novagen) in accordance with the manufacturers instructions. 0.2 µM each of the M13rev (5' GGAAACAGCTATGACCATGA 3') (SEQ ID NO: 247) forward and Mycseq (5' CTCTTCTGAGAT-GAGTTTTTG 3') (SEQ ID NO: 248) reverse primers were used. 5 µl of a 1:10 dilution of a stationary phase bacterial culture was used as the template for a final reaction volume of 20 µl. The cycling conditions used were a 2 minute hot start at 94° C., 25 cycles of denaturation at 94° C. (1 minute), primer annealing at 42° C. (30 seconds) and extension at 72° C. (1 min), followed by a final 5 minute extension at 72° C. PCR products were verified by agarose gel electrophoresis and cleaned up with ExoI/SAP (shrimp alkaline phosphatase) prior to sequencing of both strands with primers 145837 (5' GGAGATTTTCAACGTGAA 3') (SEQ ID NO: 249) and 142051 (5' CTCTTCTGAGATGAGTTTTTTG 3') (SEQ ID NO: 250). The closest human germlines of the  $V_H$  and  $V_L$ segments were determined (Table 4).

TABLE 4

$V_H$ and $V_L$ germlines of ERBB2 clones			
Mab	Human $V_H$ germline gene	Human $V_L$ germline gene	
S1R2A_CS_1F7	1-02 (DP8/75)	$V\lambda$ 3h	
S1R2A_CS_1D11	1-69 (DP10)	$V\lambda \ 1b \ (DPL5)$	
S1R2C_CS_1D3	1-69 (DP10)	$V\lambda \ 1b \ (DPL5)$	
S1R2C_CS_1H12	3-48 (DP51)	$V\lambda \ lc \ (DPL2)$	
S1R2A_CS_1D3	1-02 (DP8/75)	$V\lambda  1g  (DPL3)$	
S1R3B2_BMV_1E1	3-33 (DP50)	$V\lambda \ 1b \ (DPL5)$	
S1R3C1_CS_1D3	6-1 (DP74)	Vλ 2c	
S1R3B2_DP47_1E8	3-23 (DP47)	$V\lambda \; 1e\; (DPL8)$	
S1R3B2_BMV_1G2	1-18 (DP14)	Vк L12	
S1R3B2_BMV_1H5	3-33 (DP50)	$V\lambda \; 2a2\; (DPL11)$	
S1R3C1_CS_1A6	5-51 (DP73)	$V\lambda \ lc \ (DPL2)$	

TABLE 4-continued

$V_H$ and $V_L$ germlines of ERBB2 clones			
Mab	Human $V_H$ germline gene	Human $V_L$ germline gene	
S1R3B2_DP47_1C9	3-23	$V\lambda1c~(DPL2)$	
S1R3B2_DP47_1E10	(DP47) 3-23 (DP47)	$V\lambda1g(DPL3)$	
S1R3C1_CS_1B10	(D147) 1-69 (DP10)	Vλ 6a	
S1R3A1_BMV_1F3	(DF10) 3-21 (DP77)	V\lambda 31 (DPL16)	
S1R3B1_BMV_1G11	3-23 (DP47)	$V\lambda \ 2a2 \ (DPL11)$	
S1R3A1_BMV_1G4	1-03 (DP25)	$V\lambda2a2\;(DPL11)$	
S1R3B1_BMV_1H11	3-23 (DP47)	Vк L12	
S1R3A1_CS_1B9	5-51 (DP73)	$V\lambda8a(DPL21)$	
S1R3B1_BMV_1H9	4-04 (DP70)	$V\lambda3l(DPL16)$	
S1R3A1_CS_1B10	1-02 (DP8/75)	$V\lambda8a(DPL21)$	
S1R3B1_BMV_1C12	3-30.5 (DP49)	$V\lambda1c~(DPL2)$	
S1R3C1_BMV_1H11	3-33 (DP50)	$V\lambda1e~(DPL8)$	
S1R3B1_BMV_1A10	(DP30) 3-30.5 (DP49)	$V\lambda3l(DPL16)$	
S1R3A1_CS_1D11	5-51	$V\lambda8a(DPL21)$	
S1R3C1_DP47_1H1	(DP73) 3-23 (DP47)	$V\lambda3h$	
S1R3A1_CS_1B12	(DP47) 1-02 (DP8 (75)	$V\lambda1e~(DPL8)$	
S1R3B1_BMV_1H5	(DP8/75) 3-33	$V\lambda3l(DPL16)$	
S1R3A1_DP47_1A6	(DP50) 3-23	$V\lambda1c~(DPL2)$	
S1R3B1_DP47_1E1	(DP47) 3-23	Vλ 6a	
S1R3B1_BMV_1A1	(DP47) 1-18 (DP14)	$V\lambda2a2~(DPL11)$	

## Example 6

# BIACORE® Binding Assay

[0192] Binding of different Her2-directed binders (antibodies and SMIPs) to monomeric Her2 ECD and truncations of dimeric Her2 ECD were determined using a BIACORE® T100 instrument (GE Healthcare, Biacore, Piscataway, N.J.). Her2-directed binders were captured by a monoclonal mouse anti-human Fc (GE healthcare), which was covalently conjugated to a carboxylmethyl dextran surface (CM4) via amines N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide using hydrochloride and N-hydroxysuccinimide. The unoccupied sites of the activated surface were blocked by ethanolamine. The capturing antibody (referred to as anti hFc) binds to the C_H2 domain of IgG Fc of all sub-classes and showed no discernible dissociation from the captured her2-binders during the course of the assay. Every cycle, 3 different Her2 binders and a non-binder (negative control) were individually captured by anti hFc on 4 different flow cells, typically to about 50 RU, followed by injection of the analyte (Her2 dimers and monomer) at a particular concentration for 10 minutes over all flow cells. The dissociation of the formed complexes were subsequently followed for 12 minutes. At the end of the cycle, the surface was regenerated gently using 3M  $MgCl_2$  which dissociates protein bound to the capturing anti hFc antibody. Multiple such cycles were performed to study binding of different analytes at different concentrations, in the range of 0-300 nM, for each set of three Her2 binders captured. Her2 binders were reproducibly captured every cycle with CV not exceeding 1%. The binding was performed at 25° C. in 0.01 M HEPES pH 7.4, 0.15 M NaCl, 0.005% v/v SURFACTANT P20. Signal associated with binding to the negative control was used to subtract for bulk refractive changes. The kinetic parameters and affinities were determined using BIAEVALUATION software.

[0193] HERCEPTIN® (trastuzumab) bound monomeric EQR, dimeric ECD and shed ECD (monomeric), weakly bound HER018 but did not bind a truncated fusion protein lacking the CR2 domain. In contrast, HER033 and HER030 bound only dimeric ECD and dimeric HER018 but did not bind monomeric EQR or shed ectodomain (ECD). Specifically for dimeric HER2 may be advantageous in that such binders may have increased selectivity for tumors and may not bind, or show reduced binding to tissues that express low levels of HER2 and/or where ligand independent homodimer formation is limited. Such HER2 binders with reduced binding to non-tumor target tissues (e.g., cardiac tissues) may, thus, have fewer side effects including lower toxicity. In addition, a lack of binding to shed HER2 ectodomain would reduce the effective dose compared to a HER2-binding agent that has significant binding to shed ECD.

**[0194]** The results of the BIACORE® assay are shown in FIG. **7**.

**[0195]** Trastuzumab and the SMIP version of trastuzumab (HER018) bind full length dimer and monomer soluble receptors similarly at low nanomolar levels (about 1 to about 5 nM), whereas truncated dimer soluble receptors (i.e., lacking all three trastuzumab contact sites) are bound poorly or not at all (see Table 5). In contrast, Her030 and Her033/Her067 SMIPs bind soluble dimer receptors at nanomolar affinities (about 4 to about 8 nM), but not monomer HER2. The HER033 and HER067SMIPs have the same amino acid sequence, but the difference between them is that the former is produced in HEK cells while the latter is produced in CHO cells. Binding by HER033 and HER067SMIPs is substantially the same. HER030 appears to bind less strongly than Her033/Her067 to the dimers.

TABLE 5

BIACORE ® binding affinity summary					
		Affinity (r	IM) at 25°	C.	
	Herceptin	Her 018	Her 033	Her 067	Her 030
SIIS (Dimer) 1.8 (Dimer) 1.6 (Dimer) SIIS (Monomer) (Her155)	1.06 228 NB 3.44	1.4 167 NB 4.59	7.23 4.92 NB 508	8.18 6.47 NB ND	35.6 27.6 NB ND

NB—No Binding Observed

ND-not enough binding to fit

## Example 7

# BrdU and ATP Proliferation Assays

[0196] To 96-well plates, cells were added at  $2.5 \times 10^3$  cells/ well (SKBR3, BT474, MDA-MB-453, MDA-MB-175) or at  $5 \times 10^3$  cells/well (MDA-MB-361). The next day, SMIPs were added to the cells at the desired concentration and then incubated at 37° C./5% CO2 for 4 (SKBR3, MDA-MB-453, MDA-MB-361, MDA-MB-175), 5 (BT474), or 7 (MDA-MB-361) days. The day before cells were harvested, 5-bromo-2'-deoxyuridine (BrdU) is added to a final concentration of 0.1 mM and continued to incubate overnight at 37° C. After incubation, media was removed and then the cells were treated with ethanol-based fix solution (DELFIA® Cell Proliferation Kit, Perkin Elmer, Waltham, Mass.) at room temperature (RT) for 30 minutes. Fix solution was removed by aspiration, 100 µl/well anti-BrdU-Eu labeled antibody (0.5 mg/mL) was added, and the cells were incubated at RT for 2 hours. Cells were then washed 4 times with Tris-based DELFIA Platewash (300 µl/well/wash). DELFIA Inducer (with Triton) X-100, glycine, HCl, and chelator) was then added to the cells (200 µl/well) and incubated with shaking for 15 minutes at RT. Fluorescence was measured using Flex Station) 3 in Time resolved fluorescence mode (Molecular Devices, Sunnyvale, Calif.).

**[0197]** After the proliferation assay fluorescence reading, the DELFIA Inducer was removed by aspiration and Hoechst 33342 nuclear stain solution (Invitrogen, Carlsbad, Calif.) was added to the cells. Nuclear stain fluorescence was measured on an IN Cell Analyzer at 4× resolution.

[0198] Alternatively, we investigated anti-Her2 SMIP antiproliferation activity in MDA-MB-361 cells as follows. MDA-MB-361 breast cancer cells were plated in 96-well format and treated with anti-Her2 or control reagents for indicated concentrations and times (24-96 hr). For proliferation assays, media (DMEM plus 10% FBS) was removed, the cells washed with phosphate-buffered saline (PBS), fixed with 4% paraformaldehyde and nuclei stained with DAPI (Molecular Probes). Stained nuclei were counted using Cellomics High Content assay measuring fluorescence at 360 nM. For apoptosis assay, fixed cells were permeabilized by treatment with 0.2% Triton 100 in PBS prior to primary staining with mouse anti-cleaved PARP antibody (Cell Signaling Technologies) and secondary staining with goat antimouse IgG labeled with ALEXA488 (Invitrogen). Fluorescence was measured in Cellomics High Content assay at 488 nM.

**[0199]** ATP Lite First Step assay (Perkin Elmer) was used to assess cellular viability by measuring ATP levels via luminescence (ATP luciferase). To 96-well plates, cells were added at  $2.5 \times 10^3$  cells/well (SKBR3, BT474, MDA-MB-453, MDA-MB-175) or at  $5 \times 10^3$  cells/well (MDA-MB-361). The next day, SMIPs were added to the cells at the desired concentration and then incubated at  $37^{\circ}$  C./5% CO₂ for 4 (SKBR3, MDA-MB-453, MDA-MB-361, MDA-MB-175), 5 (BT474), or 7 (MDA-MB-361) days. After SMIP incubation for the desired amount of time, lyophilized ATP Lite substrate is reconstituted with 10 ml of ATP Lite substrate/lysis solution and allowed to sit at room temperature for 10 minutes. This reconstituted substrate solution was added to the cells (100 µl/well) and read luminescence on Top Count Reader (Packard).

**[0200]** The results of the proliferation assays are shown in FIGS. **10-12**.

## Example 8

#### Pathway Phosphorylation Assays

[0201] To 96-well plates, cells were added at  $8-12 \times 10^3$  cells/well depending on cell type (Becton-Dickinson, San

Jose, Calif.) and allowed to incubate overnight in growth medium with serum at 37° C./5% CO2. After removal of growth medium, the cells were washed with serum-free medium, aspirated, and then serum-free media was added for incubation at 37° C./5% CO2 for 3 hours. The SMIP of interest was prepared in prewarmed serum-free media, added to each well at the indicated concentration, and incubated at 37° C./5% CO₂ for desired time points. As a control, signaling was inhibited with AG825 (Calbiochem, LaJolla, Calif.) at 40  $\mu M; LY294002$  (Cell Signaling) at 50  $\mu M;$  or U0126 MEK1/2 inhibitor (Cell Signaling) at 10 µM. The cells were then fixed in formaldehyde (diluted in 1×PBS) at a final concentration of 3.7% for 10 minutes at 37° C./5%  $CO_2$ . The cells were then washed two times with PBS. After removing the PBS, the cells were permeabilized in 0.1% Triton® X-100 (Sigma-Aldrich, St. Louis, Mo.) solution diluted in 1×PBS at room temperature for 5 minutes. The cells were then washed two times with PBS and blocked by incubation in PBS/1% BSA (Sigma-Aldrich) at room temperature for 30 minutes (or overnight at 4° C.).

[0202] The blocking solution was removed and primary antibody (in PBS with 3% horse serum or PBS with 1% BSA, and 0.1% Triton® X-100) was added for 1 hour at room temperature (or overnight at 4° C.). The primary antibodies used (at 0.125 µg/well) were (1) rabbit anti-phospho-akt (Ser473) (Cell Signaling, Danvers, Mass.); (2) mouse antiphospho-Erkl/2 (Cell Signaling, Danvers, Mass.); and (3) rabbit anti-phospho-ErbB2 (Abgent, San Diego, Calif.). The primary antibody was removed and the cells were washed 3 times with PBS. The secondary antibody (in PBS with 3% horse serum or PBS with 1% BSA, and 0.1% Triton® X-100) was then added for 1 hour at room temperature (or overnight at 4° C.) protected from light. The secondary antibodies used (at 0.2 µg/well) were Alexa 488 donkey anti-rabbit IgG (Invitrogen, Carlsbad, Calif.) and DyLight 649 goat anti-ms IgG (Pierce, Rockford, Ill.). The secondary antibody was removed and the cells were washed 3 times with PBS. Then  $100 \,\mu\text{L}$  of PBS containing 200 ng/ml Hoechst 33342 nuclear stain (Invitrogen, H3570) (and if needed 1 ug/ml Cell Mask Blue cytoplasmic stain (Invitrogen, H34558) was added to the cells. The plates were covered and kept protected from light. The plates were then imaged.

[0203] Alternatively, we investigated anti-Her2 SMIP signal transduction activity in MDA-MB-361 cells as follows. MDA-MB-361 breast cancer cells, were plated in 6-well plate to 80-90% confluency (DMEM plus 10% FBS) and treated with anti-Her2 or control reagents for 24 hr with and without pretreatment with Heregulin (HRG-15 min.) or EGF (30 min.). For assay of total and phosphorylated Her2, cells were lysed, 50 ug total protein was fractionated using SDS-PAGE and transferred to nitrocellulose membranes using standard procedures. Western blot analysis used either rabbit anti-Her2 antibody (Cell Signaling Technologies), anti-pHer2_Y1248 (Upstate) or anti-Actin (Santa Cruz) as primary antibody and subsequently stained with HRP-conjugated anti-rabbit IgG. Peroxidase activity was measured using ECLplus2 kit (GE Healthcare) following manufacturer's protocols and exposed to film. As shown in FIG. 13, HER033 induces HER2 phosphorylation.

**[0204]** To measure increased downstream phosphoprotein signal transduction, MDA-MB-361 breast cancer cells were plated in 96-well format and treated with anti-Her2 or control reagents for the concentrations and times (10 min to 24 hr) shown in FIG. **15**. Media was removed, cells washed with

PBS, fixed with 4% paraformaldehyde, and permeabilized with 0.2% Triton 100/PBS. Cells were subsequently stained with either rabbit anti-pAKT (Cell Signaling Technologies), anti-pERK (Cellomics), anti-pS6K (Cell Signaling Technologies), or anti-p38MAPK (Cell Signaling Technologies). Following PBS wash (3×), cells were stained with secondary goat anti-rabbit IgG antibody labeled with ALEXA594. Cell fluorescence was quantified using Cellomics High Content assay at 594 nM.

[0205] Her067 (Her033) has agonistic activity (increased signaling) compared to trastuzumab (see Table 6). Moreover, Her067 and Her018 are generally a stronger inducer of Her2, Erk1/2, and Akt phosphorylation than trastuzumab. The increase was statistically significant as compared to the mock treatment when measured by the pairwise student T-test (<0. 001).

TABLE 6

Induction of phosphorylation by HER018, HER067, Herceptin and Heregulin					
MDA-MB-361(JL)	HER018	HER067	Herceptin	Heregulin	
phospho-ErbB2	++	++	+	+	
phospho-Erk1/2	+	++	+	+	
phospho-Akt	+	+	+	++	

# Example 9

# Cell Cycle Assay

[0206] To investigate the effect of the ErbB2 ECD binder on cell cycle in HERCEPTIN® sensitive and HERCEPTIN® resistant cells, each well of a 6 well plate was seeded with 2×10⁵ cells (SKBR3 or BT474 (sensitive) or MDA-MB-453 or MDA-MB-361 (resistant) and incubated overnight at 37° C./5% CO₂. Cells were then treated with antibody or SMIP (at 10 µg/ml final) (in triplicate) and incubated for another 24 or 48 hours. After incubation, the cells were pulsed with 50 uM BrdU (Sigma) for 30 minutes at 37° C., the media was removed, and the cells were treated with trypsin and harvested in a FACS tube on ice. The cells were washed with PBS, fixed with 70% cold ethanol, and incubated on ice for 30 minutes. The ethanol was removed and then 2N HCl/0.5% Triton X-100 was added, and the cells were incubated for 30 minutes at room temperature (RT). The acid was removed and neutralized with 0.1 M Na₂B₄O₇ for 15 min at RT. The neutralization buffer was removed, FITC labeled anti-BrdU antibody was added (BD Bioscience) in PBS/0.5% TWEEN® 20/1% BSA, and the cells were incubated for 30 minutes at RT in the dark. The FITC dye was removed, the cells washed, and then DAPI nuclear stain (Invitrogen) and RNAse A (Qiagen) each at 1:1000 dilution was added and the cells were incubated 15 minutes in the dark and then analyzed by FACS. Statistical analysis of the data was performed using ANOVA and Student's t-test.

**[0207]** The results are presented in FIGS. **17** and **18**. We observed an increased number of cells in the G1 phase in HERCEPTIN® treated SKBR3, BT474 and MDA-MB-453 cells. Among cells treated with HER033 SMIP, we observed an increased number of cells in S phase in SKBR3 and BT474 cells.

#### Example 10

## In Vivo Xenograft Assay

**[0208]** To investigate the effect of the ErbB2 binding molecules of the invention in vivo, we tested the molecules in three mouse models.

## [0209] SCID/Beige Mouse Model

**[0210]** Female (6-7 week old) Beige SCID mice (Beige SCID CB-17/IcrHsd-Prkdcscid-Lystbg) were obtained from Harlan Sprague Dawley, N.J. Virus free MDA-MB-361 cells were thawed from a new vial and cultured to generate appropriate numbers. Cells were grown to near confluency and had a viability of >90%. Cells were harvested, washed twice with sterile PBS, resuspended to  $2 \times 10^8$  cells/ml, then combined with Matrigel 1:2. and kept on ice until injection.

**[0211]** Tumor Cell Implantation and Monitoring: Each mouse was injected with 100  $\mu$ l of the cell/Matrigel suspension (1×10⁷ cells) subcutaneously on the right flank. Mice were monitored daily for tumor growth. Tumors were established when they reached about 150 to about 300 mm³ (Volume=½[length×(width)²). Tumors developed in 100% of the implanted mice. Mice were sorted into groups according to tumor size, keeping means consistent among groups using LabCat software. Sorting occurred on day 0, which was the same day the mice received their first treatment.

**[0212]** Mice were monitored (i.e., weighed and tumors measured) two to three times weekly. Mice were sacrificed if ulceration of tumor occurred, extreme body weight loss (greater than or equal 20%), tumor exceeded about 1200 to about 1500 mm³, or tumor inhibited mobility of a mouse. The study is continued for a total of about 60 days.

**[0213]** Treatment: Mice were sorted into three groups of 11 mice each. Treatment began on day 0 (about six days after cell implantation). Each mouse of a group received intraperitoneal treatments twice a week (for a total of five treatments), which were given in equimolar amounts (900 nM) of (1) SMIP HER067 (100  $\mu$ g), (2) Herceptin (136  $\mu$ g, positive control), or (3) human IgG (136  $\mu$ g, negative control). Survival and tumor size was recorded two to three times weekly. Results were graphed (+/–SEM) and analyzed using Prism software (see FIGS. **21** and **22**).

[0214] BALB/c nu and nu/nu Mouse Models

**[0215]** Male BALB/c nu/nu (nude) mice (18-23 g) and female nu/nu (nude) mice (18-23 g) were obtained from Charles River Laboratories, Wilmington, Mass.

[0216] Subcutaneous BCL Xenografts:

[0217] Female, athymic nude mice were exposed to total body irradiation (400 rads) to further suppress their residual immune system and facilitate the establishment of xenografts. Three days later, the irradiated mice were injected subcutaneously (SC) with  $1 \times 10^7$  MDA-MB-361 cells in Matrigel (Collaborative Biomedical Products, Belford, Mass., diluted 1:1 in culture medium) in the dorsal, right flank. When the tumors reached the mass of 0.1 to 0.25 g, the tumors were staged to ensure uniformity of the treatment groups. Male, athymic Balb/c nude mice were injected s.c. with  $1 \times 10^7$  cells in the right flank. When tumors reached an average tumor mass of 0.1 to 0.25 g, the tumors were staged to ensure uniformity of the treatment groups. Mice were staged to ensure uniformity of the treatment mass of 0.1 to 0.25 g, the tumors were staged to ensure uniformity of the treatment groups. Male, athymic Balb/c nude mice were injected s.c. with  $1 \times 10^7$  cells in the right flank. When tumors reached an average tumor mass of 0.1 to 0.25 g, the tumors were staged to ensure uniformity of the treatment groups. Mice were

dosed with compounds (100 µg/mouse ip) on days 1, 4, 6, 8 and 11 (n=10 mice/treatment group). All compounds were administered ip. Tumors were measured at least once a week and their mass (±SEM) was calculated. Tumor mass for each treatment group was compared to that from the vehicletreated group for statistical significance using ANOVA and subsequent pairwise comparisons to the vehicle-treated group using a one-tailed t-test with the error term for the t-test based on the pooled variance across all treatment groups. The results are shown in FIGS. **19** and **20**.

**[0218]** The preliminary results in vivo as shown in FIGS. **19-22** are inconclusive. A number of factors could contribute to the differences observed in the three mouse models and are being further investigated. For example, while not intending to be limiting, the different experiments were dosed differently (twice weekly as compared to every other day, which means the former dosing lasted over a longer period of time, the tumors in the vehicle control groups in some of the experiments did not grow particularly well, and the mouse backgrounds had differing effector functionality (i.e, the nu/nu nude mice have B cells and NK cells, while the SKID/Beige mice have macrophages and monocytes. Based on the in vitro and in vivo results taken as a whole, the anti-ErbB2 binding proteins are believed to be efficacious in treating tumors.

**[0219]** The specification is most thoroughly understood in light of the teachings of the references cited within the specification. The embodiments within the specification provide an illustration of embodiments of the invention and should not be construed to limit the scope of the invention. The skilled artisan readily recognizes that many other embodiments are encompassed by the invention. All publications and patents cited in this disclosure are incorporated by reference in their entirety. To the extent the material incorporated by reference contradicts or is inconsistent with this specification, the specification will supercede any such material. The citation of any references herein is not an admission that such references are prior art to the present invention.

**[0220]** Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the application, are to be understood as being modified in all instances by the term "about." Accordingly, unless otherwise indicated to the contrary, the numerical parameters are approximations and may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

**[0221]** Unless otherwise indicated, the term "at least" preceding a series of elements is to be understood to refer to every element in the series. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein.

SEQUENCE TABLE

Her2_S1R2A_CS_1F7

 $[\]rm V_{\it H}$  with CDR1, CDR2 and CDR3 underlined EVQLVQSGAEVKKPGASVKVSCKASGYTFT<u>GYYMH</u>WVRQAPGQGLEWMGWINP <u>NSGGTNYAQKFQGW</u>VTMTRDTSISTAYMELSRLRSDDTAVYYCAR<u>DSTMAPGAF</u> DIWGRGTLVTVSS (SEQ ID NO: 1)

V_L with CDR1, CDR2 and CDR3 underlined QSVLTQPPSVSVAPGQTARMTC<u>GGNNIESKTVH</u>WYQQKPGQAPVLVVY<u>NDNVRP</u> <u>S</u>GIPARFSGSNSGNTATLTINRVEAGDEADYYC<u>QVWDSSRDQGV</u>FGGGTKLTVLGA (SEQ ID NO: 2)

## Her2_S1R2A_CS_1D11

V_H with CDR1, CDR2 and CDR3 underlined EVQLVQSGSEVRRPGSSVRVSCTASGDTSSSFTVNWLRQAPGQGLEWMG<u>GITPM</u> <u>FGTANYAQMFED</u>RVTITADEMELSGLTSEDTAVYFCAT<u>GPSDYVWGSYRFLDT</u>WG RGTTVTVSS (SEQ ID NO: 3)

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined QAVLTQPSSVSAAPGQEVSISC<u>SGARSNVGGNYVS</u>WYQHLPGTAPKLLIY<u>DNNKR</u> PSGMPDRFSGSKSGTSATLGITGVQTEDEADYYC<u>ATWDSSLSAVV</u>FGGGTKLTVL GA

(SEQ ID NO: 4)

#### Her2_S1R2C_CS_1D3

V_H with CDR1, CDR2 and CDR3 underlined QVQLVQSGSEVRRPGSSVRISCTASGDTSS<u>SFTVN</u>WVRQAPGQGLEWMGGITPM <u>FGTANYAQVFED</u>RVTIIADEMELSGLTSEDTAVYFCAT<u>GPSDYVWGSYRFLDR</u>WG RGTLVTVSS (SEQ ID NO: 5)

V_L with CDR1, CDR2 and CDR3 underlined QSVLTQPPSVSAAPGQKVTISC<u>SGGRSSIGNNYVS</u>WYQHLPGTAPKLLIY<u>DNNQRP</u> <u>S</u>GIPDRFSGSKSGTSATLGITGLQTGDEADYYC<u>GTWDSSLSAVV</u>FGGGTKVTVLGA (SEQ ID NO: 6)

## Her2_S1R2C_Cs_1H12

V_H with CDR1, CDR2 and CDR3 underlined EVQLVETGGGLVQPGGSLRLSCAASGFTFS<u>SYGMN</u>WVRQAPGKGLEWVS<u>YISSS</u> <u>GNTIFYADSVKG</u>RFTISRDSAKNSVSLQMNSLRDEDTAVYYCAS<u>YYSYYYGM</u>DAW GQGTMVTV (SEQ ID NO: 7)

V_L with CDR1, CDR2 and CDR3 underlined SYVLTQPPSASGTPGQRVTISC<u>SGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRP</u> <u>S</u>GVPDRFSGSKSGTSASLAISGLRSEDEADYYC<u>AAWDYSLSGWV</u>FGGGTKVTVLGA (SEQ ID NO: 8)

Her2_S1R2A_CS_1D3

V_H with CDR1, CDR2 and CDR3 underlined EVQLVQSGAEVKKPGASVKVSCKASGYSFT<u>AFYIH</u>WVRQAPGQGLEYLG<u>WIDPNT</u> <u>GATKYAQRFQG</u>RVIMTWDTSITTATMELSRLTSDDSAVYYCVR<u>DLREWGYELSVE</u> <u>YWGRGTLVTVSS</u> (SEQ ID NO: 9)

V_L with CDR1, CDR2 and CDR3 underlined QSVLTQPPSASGTPGQRVTISC<u>SGSSSNIGSNYVY</u>WYQQLPGTAPKLLIY<u>RNNQRP</u> <u>S</u>GVPDRFSGSKSGTSASLAISGLRSEDEADYYC<u>AAWDDSLSGWV</u>FGGGTKLTVLGA (SEQ ID NO: 10)

Her2_S1R3B2_BMV_1E1

 $\rm V_{\it H}$  with CDR1, CDR2 and CDR3 underlined EVQLVETGGGVVQPGGSLSLSCAASGFTFSSYGMQWVRQAPGKGLEWVAFIRYD GSSEYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCGRTLESSLWGKGT LVTVSS

(SEQ ID NO: 11)

V_L with CDR1, CDR2 and CDR3 underlined QSVLTQPPSVSAAPGQKVTISC<u>SGSTSNIGNNYVS</u>WYQQHPGKAPKLMIY<u>DVSKRP</u> <u>S</u>GVPDRFSGSKSGNSASLDISGLQSEDEADYYC<u>AAWDDSLSEFL</u>FGTRTKLTVLGA (SEQ ID NO: 12)

Her2_S1R3C1_CS_1D3

V_H with CDR1, CDR2 and CDR3 underlined QVQLQESGPGLVKPSQTLSLTCGISGDSVS<u>SNSAAWN</u>WIRQSPTRGLEWLG<u>RTYY</u> <u>RSSWYHNYAPSMNSR</u>LTIIADTSKNQFSLQLNSVTPEDTAVYYCAS<u>GWAFDV</u>WGR GTLVTVSS (SEQ ID NO: 13)

 $V_L$  with CDR1, CDR2 and CDR3 underlined QSVLTQPPSASGSPGQSVTISCTGTSSDVGAYDPVSWYQQHPGKAPKLMIY<u>EVNK RPS</u>GVPDRFSGSKSGNTASLTVSGLQAEDEADYYC<u>SSYAGSKNLL</u>FGGGTKLTVL GA

(SEQ ID NO: 14)

Her2_S1R3B2_DP47_1E8

V_H with CDR1, CDR2 and CDR3 underlined EVQLLESGGGLVQPGGSLRLSCAASGFTES<u>SYAMS</u>WVRQAPGKGLEWVS<u>AISGS</u> <u>GGSTYYADSVKG</u>RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR<u>QSGADWYFDL</u>W GRGTLVTVSS (SEQ ID NO: 15)

 $V_L$  with CDR1, CDR2 and CDR3 underlined QAVLTQPSAVSGAPGGRVTISC<u>TGTSSNIGTNYLVH</u>WYQQRPGTAPQLLVS<u>GNNT</u> <u>RPS</u>GVTDRFSVSKSATSASLAITGLQAEDEADYYC<u>QTYDINLRVWV</u>FGGGTKVTVL GA

(SEQ ID NO: 16)

#### Her2_S1R3B2_BMV_1G2

V_H with CDR1, CDR2 and CDR3 underlined QVQLVQSGAEVKKPGSSVKVSCKASGYTFT<u>SYGIS</u>WVRQAPGQGLEWMG<u>WISAY</u> <u>MGNTNYAQKLQG</u>RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR<u>VPGVSGSYPDY</u> <u>YYMD</u>VWGKGTLVTVSS (SEQ ID NO: 17)

VL with CDR1, CDR2 and CDR3 underlined DIQMTQSPSTLSASIGDRVTITC<u>RASEGIYHWLAWYQQKPGKAPKLLIYKASSLASG</u> APSRFSGSGSGTDFTLTISSLQPDDFATYYC<u>QQYSNYPLT</u>FGGGTKLEIKRA (SEQ ID NO: 18)

Her2_S1R3B2_BMV_1H5

 $V_{H}$  with CDR1, CDR2 and CDR3 underlined EVQLVQSGGGLVRPGGSLRLSCAASGFSFSDYYMTWIRQIPGKGLEWVAVIWNDG SDRYYADSVKGRFTISRDNSKNTLFLQMSSLRDEDTALYYCVRGGPTASSGFDYW GRGTLUTVSS (SEQ ID NO: 19)

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined SSELTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYLQHPGKAPKLMIYEGSKR PSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTTRSTRVFGGGTKLTVLGA (SEQ ID NO: 20)

Her2_S1R3C1_CS_1A6  $\underline{V}_H$  with CDR1, CDR2 and CDR3 underlined

EVQLVQSGAEVKKPGESLKISCKGFGYNFR<u>SAWIG</u>WVRQMPGKGLEWMG<u>VIYPG</u> <u>DSDVRYSPSFQQQ</u>VTISADKSISTAYLQWSSLKASDTAMYYCTR<u>PVGQWVDSDY</u>W GKGTLVTVSS (SEQ ID NO: 21)

VL with CDR1, CDR2 and CDR3 underlined QSVLTQPPSASGTPGQRVTISC<u>SGSSSNIGTNTVNwVQQLPGTAPKLLIYTSNQRP</u> <u>S</u>GVPARFSASNSGTSASLAISGLRSEDEADYY<u>CAAWDDKLSGAV</u>FGGGTKLTVLGA (SEO ID NO: 22)

Her2_S1R3B2_DP47_1C9

V_H with CDR1, CDR2 and CDR3 underlined EVQLLESGGGLVQPGGSLRLSCAASGFTFS<u>SYAMS</u>WVRQAPGKGLEWVS<u>AISGS</u> <u>GGSTYYADSVKG</u>RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR<u>WRPLLDYHFDQ</u> WGQGTMVTVSS (SEQ ID NO: 23)

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined QSVLTQPPSASGTPGQTVTISCSGSSSNIGSSVVNWYQQPPGTAPKVLVYSNTQR PSGVPDRFSGSRSGTSASLAISGLQSEDEADYYCLAWDASLNGWVFGGGTKLTVL GA

(SEQ ID NO: 24)

Her2_S1R3B2_DP47_1E10

V_H with CDR1, CDR2 and CDR3 underlined EVQLLESGGGLVQPGGSLRLSCAASGFTFS<u>SYAMS</u>WVRQAPGKGLEWVS<u>AISGS</u> <u>GGSTYYADSVKG</u>RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR<u>GYSGYDDPDS</u>W GRGTTVTVSS (SEQ ID NO: 25)

(SEQ ID NO: 25)

 $V_L$  with CDR1, CDR2 and CDR3 underlined  $HVILTQPPSTSGTPGQTVTISC\underline{SGSSSNIGSHYVYWYQQLPGTAPKLLIY\underline{RNNQRPS}$  GVPDRFSGSKSGTSASLAISGLRSEDETDYYC<u>AAWDDSLSGRV</u>FGTGTKLTVLGA (SEQ ID NO: 26)

#### Her2_S1R3C1_CS_1B10

 $V_{H}$  with CDR1, CDR2 and CDR3 underlined QVQLQQSGAEVKKPGSSVKVSCKASGGTIS<u>NYAIS</u>WVRLAPGQGLEWMG<u>SIVPLH</u> <u>GTTNFAQKFQG</u>RVTITADESTSTSYMEVNVLTYEDTAMYYCAS<u>LNWGY</u>WGRGTLV TVSS (SEQ ID NO: 27)

V_L with CDR1, CDR2 and CDR3 underlined NFMLTQPHSVSESPGKTVTISC<u>TGSSGSIASNYVQ</u>WYQQRPDSAPTTVIY<u>EDNRRS</u> <u>S</u>GVPDRFSGSIDSNSASLSISGLKTEDEADYYC<u>QSYDSSGHVV</u>FGGGTKLTVLGA (SEQ ID NO: 28)

## Her2_S1R3A1_BMV_1F3

V_H with CDR1, CDR2 and CDR3 underlined EVQLVESGEGLVKPGGSLRLSCTASGFTFR<u>SYSLN</u>wVRQAPGQGLEWVS<u>SISSTS</u> <u>TYIYYADSVKG</u>RFTISRDDAKNTLYLQMNSLRAEDTAAYYCVR<u>LGSGGGYFPDY</u>W GRGTLVTVSS (SEQ ID NO: 29)

V_L with CDR1, CDR2 and CDR3 underlined SSELTQDPAVSVALGQTVRITC<u>QGDSLRSYYAS</u>WYQQKPGQAPVLVIY<u>GKNNRPS</u> GIPDRFSGSSSGNTASLTITGAQAEDEADYYC<u>NSRDSSGNHVV</u>FGGGTKLTVLGA (SEQ ID NO: 30)

Her2_S1R3B1_BMV_1G11

V_H with CDR1, CDR2 and CDR3 underlined QVQLVQSGGGLVQPGGSLRLSCAASGFTFS<u>TYAMS</u>WARQAPGKGLEWVS<u>SISGD</u> <u>GGRILDADSAKG</u>RFTISRDNSKNTLYLQMNGLRVEDTALYYCAR<u>ADGNY</u>WGRGTM VTVSS (SEQ ID NO: 31)

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined QSVLTQPASVSGSPGQSITISC<u>TGTSSDVGGYNYVS</u>WYQQHPGKAPKLMIY<u>EGSK</u> <u>RPS</u>GVSNRFSGSKSGNTASLTISGLQAEDEADYYC<u>SSYTTRSTRV</u>FGGGTKLTVLGA (SEQ ID NO: 32)

Her2_S1R3A1_BMV_1G4

V_H with CDR1, CDR2 and CDR3 underlined QVQLVESGAEVKKPGASVKVSCKASGYTFT<u>SYDIN</u>WVRQAPGQRLEWMG<u>WINAG</u> <u>NGNTKYSQKFQG</u>RVTITRDTSASTAYMELRSLRSDDTAVYYCAR<u>GRSYGHPYYFD</u> <u>YWGQGTLVTVSS</u> (SEQ ID NO: 33)

V_L with CDR1, CDR2 and CDR3 underlined QSVLTQPASVSGSPGQSITISC<u>TGTSSDVGGYNYVS</u>WYQQHPGKAPKLMIY<u>EGSK</u> <u>RPS</u>GVSNRFSGSKSGNTASLTISGLQAEDEADYYC<u>SSYTTRSTRV</u>FGGGTKLTVLGA (SEQ ID NO: 34)

Her2_S1R3B1_BMV_1H11

V_H with CDR1, CDR2 and CDR3 underlined EVQLVQSGGGLVKPGGSLRLSCAASGFTFS<u>SYGMH</u>WVRQAPGKGLEWVA<u>GIFYD</u> <u>GGNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGYYMDVW</u> GKGTTVTVSS (SEQ ID NO: 35)

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined QSVLTQPPSVSGAPGQRVTISCTGRSSNIGAGHDVHWYQQLPGTAPKLLIYGDSN RPSGVPDRFSGSRSGTSASLAITGLQAEDEADYYCQSYDSSLRGSVFGGGTKVTV LGA

(SEQ ID NO: 36)

Her2_S1R3A1_CS_1B9

V_H with CDR1, CDR2 and CDR3 underlined KVQLVQSGTEVKKPGESLKISCQGSGYRFS<u>SDW1A</u>WVRQMPGKGLEWMG<u>IVYPG</u> DSDTRYSPSFQGQVTISADKSISTAYLQWSGLKASDTAKYYCAR<u>VQQAVGAKGYA</u> MDVWGKGTLVTVS (SEQ ID NO: 37)

VL with CDR1, CDR2 and CDR3 underlined QTVVIQEPSFSVSPGGTVTLTCGLSSGSVSTSYYPSWYRQTPGQAPHTLIHNTKIRS SGVPDRFSGSILGNNALTITGAQADDESDYYCLLYMGSGIYVFGGGTKLTVLGA (SEQ ID No: 38)

## Her2_S1R3B1_BMV_1H9

V_H with CDR1, CDR2 and CDR3 underlined QVQLQESGAGLVKPSGTLSLTCAVSGGSIS<u>SGNWWS</u>WVRQPPGKGLEWIG<u>EISHS</u> <u>GSTNVNPSLKS</u>RVTISVDKSKNQFSLNLSSVTAADTAVYYCAR<u>VRGTVGDTRGPDY</u> WGQGTLVTVSS (SEQ ID NO: 39)

V_L with CDR1, CDR2 and CDR3 underlined SSELTQDPAVSVALGQTVRITC<u>QGDSLRSYYASWYQQ</u>KPGQAPVLVIY<u>GKNNRPS</u> GIPDRFSGSSSGNTASLTITGAQAEDEADYYC<u>NSRDSSGNHVV</u>FGGGTKLTVLGA (SEQ ID NO: 40)

#### Her2_S1R3A1_CS_1B10

 $V_{H}$  with CDR1, CDR2 and CDR3 underlined EVQLVQSGAEVKKPGASVRVSCKGSGNTFTGHY1HWVRQAPGQGLEWLGWIDPNTGDIQYSENFKGSVTLTRDPSINSVFMDLIRLTSDDTAMYYCAREGAGLANYYYYGL $<math display="inline">\underline{DVWGRGTMVTVSS}$  (SEQ ID NO: 41)

V_L with CDR1, CDR2 and CDR3 underlined QTVVLQEPSFSVSPGGTVTLTC<u>GLNFGSVSTAYYPS</u>WYQQTPGQAPRTLIY<u>GTNIR</u> <u>SS</u>GVPDRFSGSIVGNKAALTITGAQTEDESDYYC<u>ALYMGSGML</u>FGGGTKVTVLGA (SEQ ID NO: 42)

#### Her2_S1R3B1_BMV_1C12

V_H with CDR1, CDR2 and CDR3 underlined EVQLVQSGGGVVQPGRSLRLSCAASGFTFS<u>SYGMH</u>WVRQAPGKGLEWVA<u>VISYD</u> <u>GSIKYYADSVKG</u>RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR<u>TGEYSGYDTSGY</u> <u>SNWGQGTLVTVSS</u> (SEQ ID NO: 43)

V_L with CDR1, CDR2 and CDR3 underlined QSVLTQPPSASGTPGQRVTISC<u>SGSSSNIGSNTVN</u>WYQRLPGAAPQLLIY<u>NNDQRP</u> <u>S</u>GIPDRFSGSKSGTSGSLVISGLQSEDEADYYC<u>ASWDDSLNGRV</u>FGGGTKLTVLG (SEQ ID NO: 44)

## Her2_S1R3C1_BMV_1H11

V_H with CDR1, CDR2 and CDR3 underlined GVQLVESGGGLVKPGGSLRLSCAASGFTFS<u>SYNMN</u>WVRQAPGKGLEWVS<u>AISGS</u> <u>GGSTYYADSVTGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDTSGWYGDGM</u> <u>DVWGRGTLVTVSS</u> (SEQ ID NO: 45)

VL with CDR1, CDR2 and CDR3 underlined DIQMTQSPSTLSASIGDRVTITCRASEGIYHWLAWYQQKPGKAPKLLIYKASSLASG APSRFSGSGSGTDFTLTISSLQPDDFATYYCQQYSNYPLTFGGGTKLEIKRA (SEO ID NO: 46)

# Her2_S1R3B1_BMV_1A10

V_H with CDR1, CDR2 and CDR3 underlined QMQLVQSGGGVVQPGR5LRLSCAASGFTES<u>SYGMH</u>WVRQAPGKGLEWVA<u>VISY</u> <u>DGSIKYYADSVKG</u>RFTISRDNSKNTLYLQMNSLRAEDTGVYYCSK<u>DRYSSGWYSS</u> <u>DAFDIW</u>GRGTMVTVSS (SEQ ID NO: 47)

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS GIPDRFSGSSSGNTASLTITGAQAEDEADYYC<u>HSRDSSGNHVL</u>FGGGTKLTVLGA (SEQ ID NO: 48)

# Her2_S1R3A1_CS_1D11

V_H with CDR1, CDR2 and CDR3 underlined EVQLVQSGAEVKKPGESLKISCKGSGYTFT<u>NHWIA</u>WVRQMPGKGLEWMG<u>IIYPGD</u> <u>SETRYSPSFQG</u>HVTISADKSISTAYLQWSTLKDSDSAMYFCVR<u>QARGWDDGRAGY</u> <u>YYSGMDA</u>WGQGTLVTVSS (SEQ ID NO: 49)

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined QAVVLQEPSFSVSPGGTVTLTCGLRSGSVSTSHYPSWYQQTPGQAPRTLIYSTNTRSGVPDRFSGSILGNKAALTITGAQADDESNYYCMLYMGSGMYVFGGGTKVTVLGA

(SEQ ID NO: 50)

# Her2_S1R3C1_DP47_1H1

V_H with CDR1, CDR2 and CDR3 underlined EVQLESSGGLVQPGGSLRLSCAASGFTFS<u>SYAMS</u>WVRQAPGKGLEWVS<u>AISGS</u> GGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVSGSHFPFFDS WGQGTMVTVSS (SEQ ID NO: 51)

V_L with CDR1, CDR2 and CDR3 underlined QSVLTQPPSVSVAPGQTARITC<u>GGDKIGHKSVH</u>WYQQKPGQAPVLLVY<u>DDRKRPS</u> GIPERFSGSNSGNTATLTISRVEAGDEAAYHC<u>QVWDRSSDPYV</u>FGTGTKVTVLGA (SEQ ID NO: 52)

# Her2_S1R3A1_CS_1B12

V_H with CDR1, CDR2 and CDR3 underlined QVQLVQSGAEVKKPGASVKVSCQASGYTFS<u>GHYMHL</u>VRQAPGQGLEWMG<u>WIHP</u> <u>TSGGTTYAQKFQG</u>RVVMTRDTSISTAYMELSRLTSDDTAVYYCAR<u>MSQNYDAFDI</u> WGQGTMVTVSS (SEQ ID NO: 53)

 $V_L$  with CDR1, CDR2 and CDR3 underlined QAVLTQPSSVSGAPGQRVTISCTGSSSNIGAGYDVNWYQQFPGTAPKIIVYGDRPS GAPDRFSGSKSGTSASLAITGLRAEDEADYYC<u>QSWDSRLSSYV</u>FGTGTKVTVLGA (SEQ ID NO: 54)

# Her2_S1R3B1_BMV_1H5

V_H with CDR1, CDR2 and CDR3 underlined QVQLQESGGGVVQPGG5LRLSCAASGFTFS<u>GYGMH</u>WVRQAPGKGLEWVA<u>SVRN</u> <u>DGSNTYYTDSVKD</u>RFTISRDNTKNTLYLQMNSLRAEDTAVYYCAK<u>SRRVMYGTSY</u> <u>YFDYWG</u>RGTLVTVSS (SEQ ID NO: 55)

 $V_L$  with CDR1, CDR2 and CDR3 underlined SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS GIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHVVFGGGTKLTVLGA (SEQ ID NO: 56)

# Her2_S1R3A1_DP47_1A6

 $\rm V_{\it H}$  with CDR1, CDR2 and CDR3 underlined EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGS

<u>GGSTYYADSVKG</u>RFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLGIDPLWSGYY TPLDYWGRGTMVTVSS (SEQ ID NO: 57)

 $\mathbf{V}_L$  with CDR1, CDR2 and CDR3 underlined  ${\tt HVILTQPPSASGTPGQRVTISC} \underline{SGSSSNIGSNSVS} {\tt WYQQLPGTAPKLLMY} \underline{{\tt TNNQRP}}$ SGVPDRFSGSKSGTSASLAISGLQSEDEADYYCATWDASLNTWVFGGGTKVTVLGA (SEO ID NO: 58)

# Her2_S1R3B1_DP47_1E1

 $\mathbf{V}_{H}$  with CDR1, CDR2 and CDR3 underlined EVQLLESGGGLVQPGGSLRLSCAASGFTFS<u>SYAMS</u>WVRQAPGKGLEWVS<u>AISGS</u>  $\underline{GGSTYYADSVKG}RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR\underline{GGSGSDY}WGQ$ GTMVTVSS (SEQ ID NO: 59)

 $\mathbf{V}_L$  with CDR1, CDR2 and CDR3 underlined  $\texttt{NFMLTQPHSVSGSPGKTVTISC} \underline{\texttt{TRSSGYIDSKYVQ}} \texttt{WYQQRPGSAPTTVIY} \underline{\texttt{EDNRRP}}$ SGVPDRFSGSIDSNSASLTISGLETEDEADYYCQSYDDTNVVFGGGTKVTVLGA (SEQ ID NO: 60)

# Her2_S1R3B1_BMV_1A1

 $\mathbf{V}_{H}$  with CDR1, CDR2 and CDR3 underlined EVQLVQSGAEVKEPGASVKVSCKASGYDFS<u>NYGFS</u>WVRQAPGQGLEWMG<u>WISS</u> YNGYTNYAQRLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDRGLGNWYF DLWGQGTLVTVSS (SEQ ID NO: 61)

 $V_L$  with CDR1, CDR2 and CDR3 underlined QSVLTQPASVSGSPGQSITISC<u>TGTSSDVGGYNYVS</u>WYQQHPGKAPKLMIY<u>EGSK</u> <u>RPS</u>GVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTTRSTRVFGGGTKLTVLGA (SEQ ID NO: 62)

# Her2_S1R2A_CS_1F7

V_L with CDR1, CDR2 and CDR3 underlined QSVLTQPPSVSVAPGQTARMTCGGNNIESKTVHWYQQKPGQAPVLVVYNDNVRP SGIPARFSGSNSGNTATLTINRVEAGDEADYYCQVWDSSRDQGVFGGGTKLTVL (SEO ID NO: 63)

# Her2_S1R2A_CS_1D11

 $V_L$  with CDR1, CDR2 and CDR3 underlined QAVLTQPSSVSAAPGQEVSISCSGARSNVGGNYVSWYQHLPGTAPKLLIYDNNKR PSGMPDRFSGSKSGTSATLGITGVQTEDEADYYCATWDSSLSAVVFGGGTKLTVL (SEQ ID NO: 64)

# Her2_S1R2C_CS_1D3

V_H with CDR1, CDR2 and CDR3 underlined  $\texttt{QVQLVQSGSEVRRPGSSVRISCTASGDTSS} \underline{\texttt{SFTVN}} \texttt{WVRQAPGQGLEWMG} \underline{\texttt{GITPM}}$ FGTANYAQVFEDRVTIIADEMELSGLTSEDTAVYFCATGPSDYVWGSYRFLDNWG RGTLVTVSS (SEQ ID NO: 65)

# Her2_S1R2C_CS_1D3

 $\mathbf{V}_L$  with CDR1, CDR2 and CDR3 underlined QSVLTQPPSVSAAPGQKVTISC<u>SGGRSSIGNNYVS</u>WYQHLPGTAPKLLIY<u>DNNQRP</u> SGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLSAVVFGGGTKVTVL (SEQ ID NO: 66)

# Her2_S1R2C_CS_1H12

 $\mathbf{V}_{H}$  with CDR1, CDR2 and CDR3 underlined EVQLVETGGGLVQPGGSLRLSCAASGFTFS<u>SYGMN</u>WVRQAPGKGLEWVS<u>YISSS</u> GNTIFYADSVKGRFTISRDSAKNSVSLQMNSLRDEDTAVYYCAS<u>YYSYYYGMDA</u>W GQGTMVTVSS (SEQ ID NO: 67)

### Her2_S1R2C_CS_1H12

V, with CDR1, CDR2 and CDR3 underlined SYVLTQPPSASGTPGQRVTISC<u>SGSSSNIGSNTVN</u>WYQQLPGTAPKLLIY<u>SNNQRP</u>

SGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDYSLSGWVFGGGTKVTVL (SEO ID NO: 68)

# Her2_S1R2A_CS_1D3

V_L with CDR1, CDR2 and CDR3 underlined QSVLTQPPSASGTPGQRVTISC<u>SGSSSNIGSNYVYWYQQLPGTAPKLLIYRNNQRP</u> <u>S</u>GVPDRFSGSKSGTSASLAISGLRSEDEADYYC<u>AAWDDSLSGWV</u>FGGGTKLTVL (SEQ ID NO: 69)

# Her2_S1R3B2_BMV_1E1

 $V_L$  with CDR1, CDR2 and CDR3 underlined QSVLTQPPSVSAAPGQKVTISCSGSTSNIGNNYVSWYQQHPGKAPKLMIYDVSKRP SGVPDRFSGSKSGNSASLDISGLQSEDEADYYCAAWDDSLSEFLFGTRTKLTVL (SEQ ID NO: 70)

# Her2_S1R3C1_CS_1D3

 $V_L$  with CDR1, CDR2 and CDR3 underlined QSVLTQPPSASGSPGQSVTISCTGTSSDVGAYDFVSWYQQHPGKAPKLMIYEVNK RPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYAGSKNLLFGGGTKLTVL (SEQ ID NO: 71)

### Her2_S1R3B2_DP47_1E8

 $V_L$  with CDR1, CDR2 and CDR3 underlined QAVLTQPSAVSGAPGQRVTISC<u>TGTSSNIGTNYLVH</u>WYQQRPGTAPQLLVS<u>GNNT</u> <u>RPS</u>GVTDRFSVSKSATSASLAITGLQAEDEADYYC<u>QTYDINLRVWV</u>FGGGTKVTVL (SEQ ID NO: 72)

### Her2_S1R3B2_BMV_1G2

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined DIQMTQSPSTLSASIGDRVTITCRASEGIYHWLAWYQQKPGKAPKLLIYKASSLASG APSRFSGSGSGTDFTLTISSLQPDDFATYYCQQYSNYPLTFGGGTKLEIK (SEQ ID NO: 73)

# Her2_S1R3B2_BMV_1H5

V_L with CDR1, CDR2 and CDR3 underlined SSELTQPASVSGSPGQSITISC<u>TGTSSDVGGYNVS</u>WYLQHPGKAPKLMIY<u>EGSKR</u> <u>PS</u>GVSNRFSGSKSGNTASLTISGLQAEDEADYYC<u>SSYTTRSTRV</u>FGGGTKLTVL (SEQ ID NO: 74)

# Her2_S1R3C1_CS_1A6

V_L with CDR1, CDR2 and CDR3 underlined QSVLTQPPSASGTPGQRVTISC<u>SGSSSNIGTNTVNWYQQLPGTAPKLLIYTSNQRP</u> <u>S</u>GVPARFSASNSGTSASLAISGLRSEDEADYYC<u>AAWDDKLSGAV</u>FGGGTKLTVL (SEQ ID NO: 75)

# Her2_S1R3B2_DP47_1C9

V_L with CDR1, CDR2 and CDR3 underlined QSVLTQPPSASGTPGQTVTISC<u>SGSSSNIGSSVVN</u>WYQQFPGTAPKVLVY<u>SNTQR</u> <u>PS</u>GVPDRFSGSRSGTSASLAISGLQSEDEADYYC<u>LAWDASLNGWV</u>FGGGTKLTVL (SEQ ID NO: 76)

### Her2_S1R3B2_DP47_1E10

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined HVILTQPPSTSGTPGQTVTISCSGSSSNIGSHYVYWYQQLPGTAPKLLIYRNNQRPS GVPDRFSGSKSGTSASLAISGLRSEDETDYYCAAWDDSLSGRVFGTGTKLTVL (SEQ ID NO: 77)

# Her2_S1R3C1_CS_1B10

VL with CDR1, CDR2 and CDR3 underlined NFMLTQPHSVSESPGKTVTISCTGSSGSIASNYVQWYQQRPDSAPTTVIYEDNRRS SGVPDRFSGSIDSNSASLSISGLKTEDEADYYCQSYDSSGHVVFGGGTKLTVL (SEQ ID NO: 78)

# Her2_S1R3A1_BMV_1F3

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS GIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHVVFGGGTKLTVL (SEQ ID NO: 79)

# Her2_S1R3B1_BMV_1G11

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined QSVLTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEGSK RPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTTRSTRVFGGGTKLTVL (SEQ ID NO: 80)

# Her2_S1R3A1_BMV_1G4

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined QSVLTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEGSK RPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTTRSTRVFGGGTKLTVL (SEQ ID NO: 81)

# Her2_S1R3B1_BMV_1H11

 $V_L$  with CDR1, CDR2 and CDR3 underlined QSVLTQPPSVSGAPGQRVTISCTGRSSNIGAGHDVHWYQQLPGTAPKLLIYGDSN <u>RPS</u>GVPDRFSGSRSGTSASLAITGLQAEDEADYYCQSYDSSLRGSVFGGGTKVTVL (SEQ ID NO: 82)

# Her2_S1R3A1_CS_1B9

V_L with CDR1, CDR2 and CDR3 underlined QTVVIQEPSFSVSPGGTVTLTC<u>GLSSGSVSTSYYPS</u>WYRQTPGQAPHTLIH<u>NTKIRS</u> <u>S</u>GVPDRFSGSILGNNAALTITGAQADDESDYYC<u>LLYMGSGIYV</u>FGGGTKLTVL (SEQ ID NO: 83)

# Her2_S1R3B1_BMV_1H9

V_L with CDR1, CDR2 and CDR3 underlined SSELTQDPAVSVALGQTVRITC<u>QGDSLRSYYAS</u>WYQQKPGQAPVLVIY<u>GKNNRPS</u> GIPDRFSGSSSGNTASLTITGAQAEDEADYYC<u>NSRDSSGNHVV</u>FGGGTKLTVL (SEQ ID NO: 84)

# Her2_S1R3A1_CS_1B10

V_L with CDR1, CDR2 and CDR3 underlined QTVVLQEPSFSVSPGGTVTLTC<u>GLNFGSVSTAYYPS</u>WYQQTPGQAPRTLIY<u>GTNIR</u> <u>SS</u>GVPDRFSGSIVGNKAALTITGAQTEDESDYYC<u>ALYMGSGML</u>FGGGTKVTVL (SEQ ID NO: 85)

# Her2_S1R3B1_BMV_1C12

V_L with CDR1, CDR2 and CDR3 underlined QSVLTQPPSASGTPGQRVTISC<u>SGSSSNIGSNTVN</u>WYQRLPGAAPQLLIY<u>NNDQRP</u> <u>S</u>GIPDRFSGSKSGTSGSLVISGLQSEDEADYYC<u>ASWDDSLNGRV</u>FGGGTKLTVL (SEQ ID NO: 86)

# Her2_S1R3C1_BMV_1H11

 $V_L$  with CDR1, CDR2 and CDR3 underlined DIQMTQSPSTLSASIGDRVTITC<u>RASEGIYHWLA</u>WYQQKPGKAPKLLIY<u>KASSLAS</u>G APSRFSGSGSGTDFTLTISSLQPDDFATYYC<u>QQYSNYPLT</u>FGGGTKLEIK (SEQ ID NO: 87)

# Her2_S1R3B1_BMV_1A10

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS GIPDRFSGSSSGNTASLTITGAQAEDEADYYC<u>HSRDSSGNHVL</u>FGGGTKLTVL (SEQ ID NO: 88)

Her2_S1R3A1_CS_1D11

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined QAVVLQEPSFSVSPGGTVTLTCGLRSGSVSTSHYPSWYQQTPGQAPRTLIYSTNT RSSGVPDRFSGSILGNKAALTITGAQADDESNYYCMLYMGSGMYVFGGGTKVTVL (SEQ ID NO: 89)

# Her2_S1R3C1_DP47_1H1

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined QSVLTQPPSVSVAPGQTARITCGGDKIGHKSVHWYQQKPGQAPVLLVYDDRKRPS GIPERFSGSNSGNTATLTISRVEAGDEAAYHCQVWDRSSDPYVFGTGTKVTVL (SEQ ID NO: 90)

# Her2_S1R3A1_CS_1B12

V_L with CDR1, CDR2 and CDR3 underlined QAVLTQPSSVSGAPGQRVTISC<u>TGSSSNIGAGYDVNWYQQ</u>FPGTAPKIIVY<u>GDRPS</u> GAPDRFSGSKSGTSASLAITGLRAEDEADYYC<u>QSWDSRLSSYV</u>FGTGTKVTVL (SEQ ID NO: 91)

# Her2_S1R3B1_BMV_1H5

 $V_L$  with CDR1, CDR2 and CDR3 underlined SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS GIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHVVFGGGTKLTVL (SEQ ID NO: 92)

# Her2_S1R3A1_DP47_1A6

V_L with CDR1, CDR2 and CDR3 underlined HVILTQPPSASGTPGQRVTISC<u>SGSSSNIGSNSVS</u>WYQQLPGTAPKLLMY<u>TNNQRP</u> <u>S</u>GVPDRFSGSKSGTSASLAISGLQSEDEADYYC<u>ATWDASLNTWV</u>FGGGTKVTVL (SEQ ID NO: 93)

# Her2_S1R3B1_DP47_1E1

V_L with CDR1, CDR2 and CDR3 underlined NFMLTQPHSVSGSPGKTVTISC<u>TRSSGYIDSKYVQ</u>WYQQRPGSAPTTVIY<u>EDNRRP</u> <u>S</u>GVPDRFSGSIDSNSASLTISGLETEDEADYYC<u>QSYDDTNVV</u>FGGGTKVTVL (SEQ ID NO: 94)

# Her2_S1R3B1_BMV_1A1

VL with CDR1, CDR2 and CDR3 underlined QSVLTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEGSK <u>RPS</u>GVSNRFSGSKSGNTASLTISGLQAEDEADYYC<u>SSYTTRSTRV</u>FGGGTKLTVL (SEQ ID NO 95)

# Her2_S1R2A_CS_1F7

### Her2_S1R2A_CS_1F7

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined CAGTCTGTGCTGACTCAGCCACCGGGTGTCAGTGGCCCCAGGACAGACGG CCAGGATGACCTGTGCGGGGAAACAACATTGAAAGTAAAACTGTGCATTGGTACC AGCAGAAGCCGGGCCAGGCCCCTGGTCGTGGTCGTCTCAAGGATAACGTCCGG CCCCTAGGGATCCCTGGCCGATCTCTGGCTCCAACTCCGGCAACACGGGCCACCCGGCCACCCTGACCACAGGGGATGAGGCCGACCAAGCGGACGAAGCCGACGAGGACCAAGCTGAC CGTC

(SEQ ID NO: 97)

Her2_S1R2A_CS_1D11

(SEQ ID NO: 98)

Her2_S1R2A_CS_1D11

(SEQ ID NO: 99)

### Her2_S1R2C_CS_1D3

# Her2_S1R2C_CS_1D3

 $V_L$  with CDR1, CDR2 and CDR3 underlined

(SEQ ID NO: 101)

# Her2_S1R2C_CS_1H12

# Her2_S1R2C_CS_1H12

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined TCTGGGACCCCCGGGCAGAGGGTCACCATCTCTTGT<u>TCTGGAAGCAGCTCCAA</u> <u>CATCGGAAGTAATACTGGTAACAGCAGCTCCCAGGAACGGCCCCCA</u> AACTCCTCATCTAT<u>AGTAATAATCAGCGGCCCCCA</u>GGGGCCCCTGACCGATTCT CTGGCTCCAAGTCTGGCACCTCAGCGCCCCGGCCATCAGTGGGCTGCGGAGGAGGAGGAGGAGGAGCAAGGGCCACCGGCCTA GGGTGTTCGGCGGGGCGCCCGAGGGCACCAAGGTCACCGTCCTA (SEQ ID NO: 103)

Her2_S1R2A_CS_1D3

 ${\rm V}_{H}$  with CDR1, CDR2 and CDR3 underlined GAAGTGCAGCTGGTGCAGTCTGGGGGCTGAGGTGAAGAAGCCTGGGGGCCTCAG

# 36

# SEQUENCE TABLE-continued

$$\label{eq:transform} \begin{split} & \mathsf{TGAAGGTCTCCTGCAAGGCTTCTGGGTACAGCTTCACC} \\ & \mathsf{GGGTGCGACAGGCCCTGGACAAGGCCTTGAGTATTTGGGA<u>TGGATCGACCCT} \\ & \mathsf{AATACTGGTGCCACAAAATATGCACAGGCCTTTC</u>AGGGCAGGGTCATCATGACC \\ & \mathsf{TGGGACACGTCCATCACCACAGCACCATGGAACTGAGCAGGCTGACGTCTGA \\ & \mathsf{CGACTCGGCCGTCTACTACTGTGTGGAGAGATTTGCGGGAGTGGGGCTACGAAT \\ & \mathsf{TGTCCGTTGAGTAT} \\ & \mathsf{TGGCGCTGACCACGACAGGGAACCCTGGTCACCGTCTCGAGT \\ & (\mathsf{SEQ} \ ID \ \mathsf{NO}: \ 104) \end{split}$$

# Her2_S1R2A_CS_1D3

# Her2_S1R3B2_BMV_1E1

### Her2_S1R3B2_BMV_1E1

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined CAGTCTGTGTTGACGCAGCCCCCCAGTGTCTGCGGCCCCAGGACAGAAGGT CACCATTTCCTGCTTGGAAGCACCCCCCAACATTGGGAATAATTATGTCTCCTGGTACCAAGCACCCAGGCAAAGCCCCAAACTCATGATTATG<u>GATGTCAGTAA GCGGCCCCCA</u>AGCCCGACCCCAAACTCATGGCATCAGGACACTCAGGCCCCGACAGCAGCAGCAGCAGCAGCAGCAGCTGGACAAGCCGACTCTGAGGATGAGGCTGACAGCTGGCAACTGTGGCAACTAGGACCAAGCT GACCGTCCTA

(SEQ ID NO: 107)

# Her2_S1R3C1_CS_1D3

 $\label{eq:VH} V_H \mbox{ with CDR1, CDR2 and CDR3 underlined} \\ CAGGTGCAGCTGCAGGAGTCGGGGTCCAGGACTGGTGAGCCCTCGCAGACCT \\ TGTCACTCACCTGTGGCATCTCCGGGGACAGTGTCTCTA<u>GCAACAGTGCTGCTTGGAACGGCAGTGGAACGAGCCTTGAGTGGGAACGGAGGGCCTGAACGAGTCGAACGACTCTATGAACGGCAGGACGAGTGGAACGAGTCCAATGAACAGTCCAATGAACAGTCGAATAACAATGCAGTTCTTTGCAACGAGTCGGACGAGTGGACCAGTCTGTGGAACGCGGGGGGCCTTTGATGT \\ ACCACCCGAGGACACGGCTGTATATTACTGTGCAAGCCGGGTGGGCCTTTGATGT \\ \\ \end{array}$ </u>

CTGGGGCAGGGGAACCCTGGTCACCGTCTCGAGT (SEO ID NO: 108)

# Her2_S1R3C1_CS_1D3

### $V_L$ with CDR1, CDR2 and CDR3 underlined

(SEQ ID NO: 109)

# Her2_S1R3B2_DP47_1E8

# $\mathbf{V}_{H}$ with CDR1, CDR2 and CDR3 underlined

GÅGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCC TGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCA<u>GCTATGCCATGACT</u> GGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCA<u>GCTATTAGTGG</u> <u>TAGTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCT</u> CCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCC

# 37

# SEQUENCE TABLE-continued

GAGGACACGGCCGTGTATTACTGTGCGAGA<u>CAGTCGGGCGCGGACTGGTACTT</u> <u>CGATCTC</u>TGGGGCCGAGGCACCCTGGTCACCGTCTCGAGT (SEQ ID NO: 110)

# Her2_S1R3B2_DP47_1E8

 $\mathbf{V}_L$  with CDR1, CDR2 and CDR3 underlined

CAGGCTGTGCTGACTCAGCCGTCCGCAGTTTCTGGGGCCCCAGGGCAGAGGG TCACCATCTCCTGC<u>ACTGGGACCAGCTCCAACATCGGGACAAACTATCTTGTAC</u> <u>ACTGGTATCAGCAACGTCCAGGAACAGCCCCCCAACTCCTGGTCACGTAAC</u> <u>AACACTCGACCCTCT</u>GGGGTCACTGAGCGGTCTCTGTCTCCAGGCTGACGATGATATTA TCAGCCTCCCTGGCCATCACTGGGCTCCAGGCTGAGGATGAGGGTGATTATTA CTGC<u>CAGACCTATGACATCTAGAGGGTTTGGGTG</u>TTCGGCGGAGGGGCCA AGGTCACCGTCCTA (SEQ ID NO: 111)

Her2_S1R3B2_BMV_1G2

(SEQ ID NO: 112)

# Her2_S1R3B2_BMV_1G2

 $\mathbf{V}_L$  with CDR1, CDR2 and CDR3 underlined

GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTATTGGAGACAGA GTCACCATCACCTGC<u>CGGGCCAGTGAGGGTATTTATCACTGGTTGGCC</u>TGGTA TCAGCAGAAGCCAGGGAAAGCTCCTAAACTCCTGATCTAT<u>AAGGCCTCTAGTTT</u> <u>AGCCAGT</u>GGGGCCCCATCAAGGTTCAGCGGCAGGGGGTCTGGGACAGATTTCA CTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGC<u>CAAC</u> <u>AATATAGTAATTATCCGCCTCACT</u>TTCGGCGGAGGGACCAAGCTGGAGATCAAA (SEO ID NO: 113)

# Her2_S1R3B2_BMV_1H5

 $\begin{array}{l} \mathbb{V}_{H} \text{ with CDR1, CDR2 and CDR3 underlined} \\ \texttt{GAGGGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTCAGGCCTGGAGGGTCCC} \\ \texttt{TGAGACTCTCCTGTGCAGCCTCGGGGATCTCCTTCAGT<u>GACTACTACATGACATCCC} \\ \texttt{GATCCGCCAGATTCCAGGGAAGGGCCGGAGTGGGCGGTTCACCATTATTGGAAT} \\ \texttt{GATGGAAGTGATAGATACTATGCAGACTCCGTGAAGGGCCGATTCACCATTCCC} \\ \texttt{AGAGACAATTCCAAGAACACGCTGTTTCTGCAAATGAGGCCGATTCACCATTCCC} \\ \texttt{AGAGACAATTCCAAGAACACGCTGTTTCTGCAAATGAGCAGCCTGAGAGAACGA} \\ \texttt{GGACCGGCTCTATATTACTGTGTGAGA<u>GGGGGGACCAACAGCTTCAAGGGAGAT} \\ \texttt{TTGACTACTGGGGCCGAGGCACCCTGGTCACCGTCTCGAG} \\ (SEQ ID NO: 114) \\ \end{array}$ </u></u>

# Her2_S1R3B2_BMV_1H5

### $\mathbf{V}_L$ with CDR1, CDR2 and CDR3 underlined

(SEQ ID NO: 115)

# Her2_S1R3C1_CS_1A6

# Her2_S1R3C1_CS_1A6

### Her2_S1R3B2_DP47_1C9

 $V_H$  with CDR1, CDR2 and CDR3 underlined

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGGTCCC TGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGC<u>AGCTATGCCATGAGC</u>T GGGTCCGCCAGGCTCCAGGAAGGGCCTGGAGTGGGTCTCA<u>GCTATTAGTGG</u> <u>TAGTGGTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCT</u> CCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCC GAGGACACGGCCGTGTATTACTGTGCGAGA<u>TGGAGGCCTCTTCTAGACTACCA</u> <u>CTTTGACCAA</u>TGGGGCCAAGGGACAATGGTCACCGTCTCGAGT (SEQ ID NO: 118)

# Her2_S1R3B2_DP47_1C9

(SEQ ID NO: 119)

# Her2_S1R3B2_DP47_1E10

# Her2_S1R3B2_DP47_1E10

 $\rm V_L$  with CDR1, CDR2 and CDR3 underined CACGTTATACTGACTCAACCGCCCTCAACGTCTGGGACCCCCGGGCAGACGGT CACCATCTTTGTTCTGGGAGCAGCTCCAACATCGGAAGTCATTATGTATATCTG GTACCAGCAGCTCCCAGGAACGGCCCCCAAACTCCTCATCTATAGGAATAATCA GCGGCCCTCAGGGGTCCGACCGATTCTCTGGGCTCCGAGGACTGGGCACCTCAG CCTCCCTGGCCATCAGTGGGCTCCGGGCTCCGAGGATCAGACTGGGACCAAGCT GACCGTCCTA

(SEQ ID NO: 121)

# Her2_S1R3C1_CS_1B10

# $\mathbf{V}_{H}$ with CDR1, CDR2 and CDR3 underlined

(552 15 110. 122)

# Her2_S1R3C1_CS_1B10

 $\mathbb{V}_L$  with CDR1, CDR2 and CDR3 underlined AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGGAGTCTCCGGGGAAGACGGT

# 39

# SEQUENCE TABLE-continued

AACCATCTCCTGCACC<u>GGCAGTAGTGGCAGCATTGCCAGCAACTATGTGCAGT</u> GGTACCAGCAGCGCCCGGACAGTGCCCCCACCACTGTCATCTAT<u>GAGGATAAT</u> <u>CGAAGATCCTCTG</u>GAGTCCCTGATCGGTTCTCTGGCTCCATCGACAGCTCCTC CAACTCTGCCTCCTCAGCATCTCTGGACTGAAGACTGAGGACGAGGCTGACT ACTACTGT<u>CAGTCCTATGATAGTAGCGGTCATGTGGTC</u>TTCGGCGGAGGGACC AAGCTGACCGTCCTA (SEQ ID NO: 123)

# Her2_S1R3A1_BMV_1F3

# Her2_S1R3A1_BMV_1F3

 $V_L$  with CDR1, CDR2 and CDR3 underlined

(SEQ ID NO: 125)

### Her2_S1R3B1_BMV_1G11

# Her2_S1R3B1_BMV_1G11

### V_L with CDR1, CDR2 and CDR3 underlined

(SEQ ID NO: 127)

### Her2_S1R3A1_BMV_1G4

### $V_H$ with CDR1, CDR2 and CDR3 underlined

CÅGGTGCAGCTGGTGGAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAG TGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACC<u>AGTTATGATATCAAC</u>T GGGTGCGACAGGCCCCCGGACAAAGGCTTGAGTGGATG<u>GGATGGATCAACGC</u> TGGCAATGGTAACACAAAATATTCACAGAAGTTCCAGGGCAGAGTCACCATTAC CAGGGACACATCCGCGGACACAGCCTACATGGAGCTGAGGAGGCTGAGATCT GACGACACGGCCGTGTATTACTGTGCGAGA<u>GGAGGAGGCTATGGCCACCGCT</u> <u>ACTACTTTGACTAC</u>TGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT (SEO ID NO: 128)

# Her2_S1R3A1_BMV_1G4

# $V_L$ with CDR1, CDR2 and CDR3 underlined

 $c\car{Gagac} c\car{Gagac} c\c$ 

CTGC<u>AGCTCATATACAACCAGGAGCACTCGAGTT</u>TTCGGCGGAGGGACCAAGC TGACCGTCCTA (SEQ ID NO: 129)

# Her2_S1R3B1_BMV_1H11

### Her2_S1R3B1_BMV_1H11

# Her2_S1R3A1_CS_1B9

 $\label{eq:VH} V_H \mbox{ with CDR1, CDR2 and CDR3 underlined} \\ AAGGGCAGCTGGGTGCAGTGTGGGAACAGAGGGTGAAAAAAGCCCGGGGAGTCTC \\ TGAAGATCTCCTGTCAGGGTTCTGGATACAGGTTAGT<u>AGTGACTGGATTGCCT \\ GGGTGCCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGATTGTCTATCC \\ TGGTGACTCTGATACCAGATATAGCCCGTCCTTCCAAGGCCAAGTCACACAGTCACAGTCACCATCTC \\ AGCCGACAAGTCCATCAGTACTGCCTACCTGCAGTGGAGCGGCCTGAAGGCCT \\ CGGACACCGCCAAGTATTACTGTCGCGAGAGTGCAACAGCCAGTGGGAGCTAAA \\ \underline{GGTTATGGCTATGGACGTC} \\ (SEO ID N0: 132) \\ \end{array}$ </u>

# Her2_S1R3A1_CS_1B9

(SEQ ID NO: 133)

# Her2_S1R3B1_BMV_1H9

# $V_H$ with CDR1, CDR2 and CDR3 underlined

CAGGTGCAGCTGCAGGAGTCGGGGGCGCAGGACTGGTGAAGCCTTCGGGGACCC TGTCCCTCACCTGCGCTGTCTCTGGTGGCTCCATCAGC<u>AGTGGTAACTGGTGG</u> <u>AGTTGGTCCGCCAGCCCCCGGGAAGGGGCTGGAATGGATTGGGAAAATCT</u> <u>CTCATAGTGGGAGCACCAACTACAACCCGTCCCCAAGAGTCGAGTCACCATAT</u> CAGTAGACAAGTCCAAGAACCAGTTCTCCCTGAACCTGAGTTCTGTGACCGCC GCGACACGGCCGTGTATTACTGTGCGAGA<u>GTAAGGGGTACGGTGGGGGGATA</u> <u>CACGGGGACCTGACTAC</u>TGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT (SEQ ID NO: 134)

# Her2_S1R3B1_BMV_1H9

# $\mathbf{V}_L$ with CDR1, CDR2 and CDR3 underlined

 $\label{eq:transform} TCGTCTGAGCTGACTCAGGACCTGGGACCAGACAGT CAGGATCACATGCCAAGGAGCAGCCCTGTGTGTCTTGTGGACAGACGTGGTACC AGGAGACAGGCCGGGAGCAGGACAGGCCCCTGTACTTGTCATCTGTGACATGGGAACACAGCGGCCCCTGTACTGTCCAGGCGAAACACAGCAGCTCCCTGGACCACGCGGAAGATCACGGGCTCAGGGGACCAGCGGGACGAGCGGAAGATGAGGCTGACTATTACTGT<u>AACT CCCGGGACAGCAGGGGACCAAGCTGGGTAACCAGGCGGAAGATGGGGACCAAGCTGAC CGTCCTA \\ \end{tabular}$ </u>

(SEQ ID NO: 135)

# Her2_S1R3A1_CS_1B10

### Her2_S1R3A1_CS_1B10

V_L with CDR1, CDR2 and CDR3 underlined

(SEQ ID NO: 137)

# Her2_S1R3B1_BMV_1C12

 $\label{eq:VH} V_H \mbox{ with CDR1, CDR2 and CDR3 underlined } \\ GAGGGCAGCTGGTGCAGTCTGGGGAGGCGTGGTCAGCCTGGGAGGCCCC \\ TGAGACTCTCCTGTGCAGCCTCTGGGAGCCTCGGAGTGGCAGCTATGGCAGCCC \\ GGGTCCCACGCCAGGCTCCAGGCAAGGGGCCGAATGAGCAGCCGATTCACCATCT \\ CGAGGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCTGA \\ GGACACGGCTGTATATCTGTGCCCGAACTGGTGAATATAGTGGCTACGATA \\ \\ \underline{CGAGTGGTTACAGCAATTGGGGCCAAGGCCACCTGGTCACCGTCTCGAGT \\ (SEQ ID NO: 138) \\ \end{array}$ 

# Her2_S1R3B1_BMV_1C12

# $\mathrm{V}_L$ with CDR1, CDR2 and CDR3 underlined

CAGTCTGTGCTGACTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGGG TCACCATCTCTTGT<u>TCTGGAAGCAGCTCCAACATCGGGAGTAACACTGTAAAC</u> GGTACCAGCGACTCCCAGGACCGGCCCCCCAACTCCTCATCTAC<u>AATAATCA</u> <u>CAGCGGCCCTCAGGGATCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCCC</u> AGGCTCCCTGGTCATCAGTGGGCTCCAGTCTGAAGATGAGCTGGATTACTACT GT<u>GCGTCATGGGATGACAGTCTGAATGGTCGGGG</u>TTCGGCGGAGGACCAA GCTGACCGTCCTA

(SEQ ID NO: 139)

# Her2_S1R3C1_BMV_1H11

# Her2_S1R3C1_BMV_1H11

# $\mathbf{V}_L$ with CDR1, CDR2 and CDR3 underlined

# Her2_S1R3B1_BMV_1A10

# 42

# SEQUENCE TABLE-continued

GGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGCAGTTATATCATA <u>TGATGGAAGTATTAAATACTATGCAGACTCCGTGAAGGGC</u>CGATTCACCATCTC CAGAGACAATTCCAAGAACACACTGTATCTACAAATGAACAGCCTGAGAGCCGA GGACACGGGCGTTTATTACTGTTCGAAA<u>GATCGCTATAGCAGTGGCTGGTACA</u> <u>GCTCCGATGCTTTTGATATT</u>TGGGGCCCGAGGGACAATGGTCACCGTCTCGAGT (SEQ ID NO: 142)

### Her2_S1R3B1_BMV_1A10

CTA (SEQ ID NO: 143)

# Her2_S1R3A1_CS_1D11

 $V_H$  with CDR1, CDR2 and CDR3 underlined GAGGGCAGGTGGTGCAGTCTGGGGCAGAGGTGAAAAAGCCCGGAGAGTCTC TGAAGATCTCCTGTAAAGGGCTCTGGATACACCTTTACC<u>AACCACTGGATCGCC</u>T GGGTGCCCCAGATGCCCGGGAAAGGCCTGGAGTGGATGGGC<u>ATCATCTATCC</u> TGGTGACTCTGAAACGAGGTACAGCCGGCCTTCCAAGGCCACGGCACCACCTC CAGCCGACAAGTCCATCAGTACCGCCTATTTGCAGTGGAGCACCCTGAAGGAC TCGGACTCCGCCATGTACTTCTGTGTGAGA<u>CAGGCCCGTGGCTGGGACGACG</u> GACCGGCTGGATATTATTATTCCGGTATGGACGCCCTGGGGCCAGGGAACCCTG GTCACCGTCTCGAGT (SEO ID NO: 144)

(--<u>E</u> -- ---,

# Her2_S1R3A1_CS_1D11

(SEQ ID NO: 145)

# Her2_S1R3C1_DP47_1H1

 $\label{eq:v_with CDR1, CDR2 and CDR3 underlined \\ GAGGGCAGCTGGTGGAGCTCGGGGAGGCTTGGGAGCCTGGGGGGGCCC \\ TGAGACTCTCCTGTGCAGCCTCGGAGCTCGGATCACCTTT<u>AGCAGCAGCAGCAGCAGGGC \\ GGGTCCCACGCCAGGCTCCAGGAAGGGGCTGGAGTGGGGTCCACCTCTACGCAGGGC \\ TAGTGGTGACACACATACTACGCAGACTCCGTGAAGGGCCGGTCACCATCT \\ CCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCC \\ GAGGACACGGCCGTGTATTACTGTGCGAGA<u>GACTCAGCGGGACCACTTTCCATT \\ CTTTGACTCCC</u>TGGGGCCAGGGGACAATGGTCACCGTCTCGAGT (SEO ID NO: 146) \\ \\ \end{array}$ </u>

### Her2_S1R3C1_DP47_1H1

### $V_L$ with CDR1, CDR2 and CDR3 underlined

(SEQ ID NO: 147)

# Her2_S1R3A1_CS_1B12

 $V_H$  with CDR1, CDR2 and CDR3 underlined

CÅGGTGCAGCTGGTGCAATCTGGGGCTGAAGTGAAGAAGCCTGGGGCCTCAG TGAAGGTCTCTTGTCAGGCTTCTGGATACACCTTCAGC<u>GGGCACTATAGCACT</u> T<u>G</u>GTGGCACAGGCCTCGGACAAGGGCTTGAGTGGATGGGG<u>TGGATCCACC</u> TACCAGTGGTGGCACAACCTATGCACAGAGTTTCAGGGCCGGGTCGTTATGA CCAGGGACACGTCCATCAGCACAGCCTACATGGAACTGAGTAGGCTGACATCT

# 43

# SEQUENCE TABLE-continued

GACGACACGGCCGTGTATTACTGTGCAAGA<u>ATGTCCCAAAACTATGATGCTTTT</u> <u>GATATC</u>TGGGGCCAAGGGACAATGGTCACCGTCTCGAGT (SEO ID NO: 148)

# Her2_S1R3A1_CS_1B12

 $V_L$  with CDR1, CDR2 and CDR3 underlined

 $\label{eq:cagc_constraint} \begin{array}{l} \mbox{CAGCCTGGACTCAGCCGTCCTCAGTGTCTGGGGCCCCAGGGCAGAGGG} \\ \mbox{CACCATCTCCTGCACTGGGACGACTCCAACATCGGGGCAGGTTATGATGTA} \\ \mbox{AACTGGTACCAACAATTTCCAGGACAGCCCCCAAAATTATCGTCTAGGGAC} \\ \mbox{CGGCCCTCA} \\ \mbox{GGGCCCCTGACGACTCCGGGCTGAGGATGAGGCTGATTATTACTGCC} \\ \mbox{AGCCTCGGACAGTCGCCTGAGGACGAGGATGAGGCTGATTATTACTGCC} \\ \mbox{AGCCTCGGACAGTCGCCTGAGTAGTTATGTC} \\ \mbox{TCGGGACAGTCGCCTGAGGAGGAGGAGGACCAAGGCC} \\ \mbox{ACCGTCCTA} \end{array}$ 

(SEQ ID NO: 149)

### Her2_S1R3B1_BMV_1H5

# Her2_S1R3B1_BMV_1H5

(SEQ ID NO: 151)

# Her2_S1R3A1_DP47_1A6

(SEQ ID NO: 152)

### Her2_S1R3A1_DP47_1A6

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined CACGTTATACTGACTCAACCGCCCTCAGCGTCTGGGACCCCCGGGCAGAGGGGT CACCATCTGTTCTGGAAGCAGCCCCCAACATCGGAAGTAATTCCGTTAGCTG GTACCAGCAGCTCCCAGGAACGGCCCCCAAACTCCTCATGTATACTAACAATCA GCGGCCCCCAGGGGCCCCCAGACTCTCGGGCACCGAGGCCCACAGGCCCCCAGGCCCCAAGGCCGATCAGGGCGGACCAACGGCCCCCGGCCCCAGGCTCCAGGCTGACGAGGGCGGACCAACG TCCACCGTCCTA

(SEQ ID NO: 153)

# Her2_S1R3B1_DP47_1E1

# Her2_S1R3B1_DP47_1E1

(SEQ ID NO: 155)

# Her2_S1R3B1_BMV_1A1

### Her2_S1R3B1_BMV_1A1

 $\rm V_L$  with CDR1, CDR2 and CDR3 underlined CAGTCTGTGCTGACTCAGCCTGCCTCCGTGTCTGGGGTCTCCTGGACAGTCGAT CACCATCTCCTGCACCAGCAGCAGTGACGTTGGTGGTTATAACTATGTCTC CTGGTACCAACAACACCACCAGGCAAAGCCCCCAAACTCATGATTTAT<u>GAGGGCA GTAAGCGGCCCCCAAGCTCGAGGACCAAGCCCCCAAGTCTGGCAAC ACGGCCCCCGACAATCTCTGGGCTCCAGGCTGAGAACGAGGCTGATAATA CTGCAGCTCCATGATACAACCAGGAGCACGAGGCTGAGACCAAGC TGGACGCTCCA</u>

(SEQ ID NO: 157)

# >HER018_CDS

aqaqccccqaqcaqcctqaqcqcqaqcqtqqqcqatcqcqtqaccattacctqccqcqcqaqccaqqatqtqaac cqqcqtqccqaqccqctttaqcqqcaqccqcaqcqqcaccqattttaccctqaccattaqcaqcctqcaqccqqaa gattttgcqacctattattgccaqcaqcattataccaccccqccqacctttgqccaqqqcaccaaaqtqgaaattaaa cgcaccgggggtggaggctctggtggcggtggctctggcggaggtggatccggtggcggatctgaagtgcag ${\tt tgcgatggattattggggccaggggcaccctggtgaccgtgagcagtgatcaggagcccaaatcttgtgaccaaaactc}$  ${\tt ctccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatg}$ ctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaatga (SEQ ID NO: 158)

#### >HER018_Protein_leader-stop

MDFQVQIFSFLLISASVIMSRGDIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAW YQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHY TTPPTFQQGTKVEIKRTGGGGSGGGGSGGGGSGEVQLVESGGGLVQPGG SLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISA DTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGGGTLVTVSSDQEPK SCDKTHTSPPCSAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK

(SEQ ID NO: 159)

# >HER018_2h7_Leader_CDS

atggattttcaagtgcagattttcagcttcctgctaatcagtgcttcagtcataatgtccagagga
(SEO ID NO: 160)

>HER018_2h7_Leader_Protein

MDFQVQIFSFLLISASVIMSRG (SEQ ID NO: 161)

# >HER018_VL_CDS

Gatattcagatgacccagagcccgagcagcctgagcggagcgtgggcgatcgcgtgaccattacctgccgcgcg agccaggatgtgaacaccgcggtggcgtggtatcagcagaaaccgggcaaagcgccgaaactgctgatttatagc gcgagctttctgtatagcggcggcgcgctttagcggcagccgcagcggcaccgatttaccctgaccattagc agcctgcagccggaagttttggcacctattattgccagcagcagcagcagccgacctttggccaggggcacc (SEQ ID NO: 162)

# >HER018_VL_Protein

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRT (SEQ ID NO: 163)

# >HER018_G4Sx4_Linker_CDS

gggggtggaggctctggtggcggtggctctggcggaggtggatccggtggcgggatct (SEQ ID NO: 164)

>HER018_G4Sx4_Linker_Protein

# >HER018_VH_CDS

# >HER018_VH_Protein

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTN GYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDY WGQGTLVTVSS (SEO ID NO: 167)

# >HER018_CSCS_Hinge_CDS

gagcccaaatcttgtgacaaaactcacacatctccaccgtgctca
(SEQ ID NO: 168)

>HER018_CSCS_Hinge_Protein EPKSCDKTHTSPPCS (SEQ ID NO: 169)

# >HER018_Fc_Stop_CDS

>HER018_Fc_Stop_Protein

APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 171)

# >HER026_CDS

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# >HER026_Protein_leader-stop

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(SEQ ID NO: 173)

>HER027_CDS

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# >HER027_Protein_leader-stop

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(SEQ ID NO: 175)

# >HER028_CDS

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# >HER028_Protein_leader-stop

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(SEQ ID NO: 177)

### >HER029_CDS

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# >HER029_Protein_leader-stop

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(SEQ ID NO: 179)

# >HER030_CDS

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# 50

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# >HER072_Protein_leader-stop

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(SEQ ID NO: 205)

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# >HER075_CDS

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# >HER075_Protein_leader-stop

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(SEQ ID NO: 230)

# >HER086_Protein_leader-stop

MEAPAQLLFLLLWLPDTTGGVQLVESGGGLVKPGGSLRLSCAASGFTFSSYNMN WVRQAPGKGLEWVSAISGSGGSTYYADSVTGRFTISRDNSKNTLYLQMNSLRAED TAVYYCAKDTSGWYGDGMDVWGRGTLVTVSSGGGGSGGGGGGGGGGGGJUJMTQ SPSTLSASIGDRVTITCRASEGIYHWLAWYQQKPGKAPKLLIYKASSLASGPSRFS GSGSGTDFTLTISSLQPDDFATYYCQQYSNYPLTFGGGTKLEIKRDVREPKSSDKT HTCPPCPAPELLGGSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK

TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK (SEQ ID NO: 231)

(512 15 10. 15

>HER087_CDS

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# >HER087_Protein_leader-stop

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(SEQ ID NO: 233)

>HER_SMIPs_huVk3_Leader_CDS

atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggt (SEQ ID NO: 234)

>HER_SMIPs_huVk3_Leader_Protein

# MEAPAQLLFLLLWLPDTTG (SEQ ID NO: 235)

>HER_SMIPs_G4Sx3_Linker_CDS

ggaggcggcggttcaggcggaggtggctctggcggtggcggaagt (SEQ ID NO: 236)

>HER_SMIPs_G4Sx3_Linker_Protein

>HER_SMIPs_SCCP_Hinge_CDS

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(SEQ ID NO: 238)

>HER_SMIPs_SCCP_Hinge_Protein

EPKSSDKTHTCPPCP (SEQ ID NO: 239)

>HER_SMIP_Fc-Stop_CDS

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>HER_SMIP_Fc_Stop_Protein

DVREPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLMGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK (SEQ ID NO: 241)

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Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser 50 55 60 Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln 65 70 75 80 Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu 85 90 95 Ser Ala Val Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Ala 100 105 110 <210> SEQ ID NO 7 <211> LENGTH: 117 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 7 Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly 10 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr 25 20 Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45 Ser Tyr Ile Ser Ser Ser Gly Asn Thr Ile Phe Tyr Ala Asp Ser Val 50 55 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Val Ser 70 75 65 80 Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys 90 85 95 Ala Ser Tyr Tyr Ser Tyr Tyr Tyr Gly Met Asp Ala Trp Gly Gln Gly 100 105 110 Thr Met Val Thr Val 115 <210> SEQ ID NO 8 <211> LENGTH: 112 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 8 Ser Tyr Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln 1 5 10 15 Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn 20 25 30 Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu 35 40 45 Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser 50 55 60 Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg 70 65 75 80 Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Tyr Ser Leu

85

66

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95

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20 25 30 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val 50 55 60 Lys Gly  $\mbox{Arg}$  Phe Thr Ile Ser  $\mbox{Arg}$  As<br/>p Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Arg Gln Ser Gly Ala Asp Trp Tyr Phe Asp Leu Trp Gly Arg Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 16 <211> LENGTH: 113 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 16 Gln Ala Val Leu Thr Gln Pro Ser Ala Val Ser Gly Ala Pro Gly Gln 10 5 15 1 Arg Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asn Ile Gly Thr Asn 20 25 30 Tyr Leu Val His Trp Tyr Gln Gln Arg Pro Gly Thr Ala Pro Gln Leu 45 35 40 Leu Val Ser Gly Asn Asn Thr Arg Pro Ser Gly Val Thr Asp Arg Phe 50 55 60 Ser Val Ser Lys Ser Ala Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu 70 75 65 80 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Asp Ile Asn 85 90 95 Leu Arg Val Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly 100 105 110 Ala <210> SEQ ID NO 17 <211> LENGTH: 125 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 17 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser 10 1 5 15 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr 30 20 25 Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 40 35 45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu 50 55 60 Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr 75 65 70 80 Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Arg Val Pro Gly Val Ser Gly Ser Tyr Pro Asp Tyr Tyr Met 105 100 110 Asp Val Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser 115 120 125 <210> SEQ ID NO 18 <211> LENGTH: 109 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 18 Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Ile Gly 5 10 1 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Gly Ile Tyr His Trp 20 25 30 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile 35 40 45 Tyr Lys Ala Ser Ser Leu Ala Ser Gly Ala Pro Ser Arg Phe Ser Gly 55 50 60 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro 70 65 75 80 Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Asn Tyr Pro Leu 85 90 95 Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala 100 105 <210> SEQ ID NO 19 <211> LENGTH: 120 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 19 Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Arg Pro Gly Gly 1 5 10 15 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asp Tyr 20 25 30 Tyr Met Thr Trp Ile Arg Gln Ile Pro Gly Lys Gly Leu Glu Trp Val 40 Ala Val Ile Trp Asn Asp Gly Ser Asp Arg Tyr Tyr Ala Asp Ser Val 50 55 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe 70 65 75 80 Leu Gln Met Ser Ser Leu Arg Asp Glu Asp Thr Ala Leu Tyr Tyr Cys

85 90 95 Val Arg Gly Gly Pro Thr Ala Ser Ser Gly Phe Asp Tyr Trp Gly Arg 100 105 110 Gly Thr Leu Val Thr Val Ser Ser 115 120 <210> SEQ ID NO 20 <211> LENGTH: 112 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 20 Ser Ser Glu Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln 1 5 10 15 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr 25 20 30 Asn Tyr Val Ser Trp Tyr Leu Gln His Pro Gly Lys Ala Pro Lys Leu 35 40 45 Met Ile Tyr Glu Gly Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe 50 55 60 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu 70 75 80 65 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Thr Arg 85 90 95 Ser Thr Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ala 100 105 110 <210> SEQ ID NO 21 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEOUENCE: 21 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu 1 5 10 15 Ser Leu Lys Ile Ser Cys Lys Gly Phe Gly Tyr Asn Phe Arg Ser Ala 25 30 20 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met 35 40 45 Gly Val Ile Tyr Pro Gly Asp Ser Asp Val Arg Tyr Ser Pro Ser Phe 55 50 60 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr 65 70 75 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys 90 95 85 Thr Arg Pro Val Gly Gln Trp Val Asp Ser Asp Tyr Trp Gly Lys Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115

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0       25       30         yr Val Tyr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu         1e Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Fro Asp Arg Phe Ser         1y Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg         5       Glu Asp Glu Thr Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu         er Gly Arg Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu Gly Ala
5       40       45         le Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser       60         ly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg       75         er Glu Asp Glu Thr Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu       90         er Gly Arg Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu Gly Ala         105       110
0       55       60         1y Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg       70         5       70       75         er Glu Asp Glu Thr Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu       90         90       90         90       95         er Gly Arg Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu Gly Ala         105       110
5 70 75 80 er Glu Asp Glu Thr Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu 5 90 95 er Gly Arg Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu Gly Ala 00 105 110
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er Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Ile Ser Asn Tyr 0 25 30
la Ile Ser Trp Val Arg Leu Ala Pro Gly Gln Gly Leu Glu Trp Met 5 40 45
ly Ser Ile Val Pro Leu His Gly Thr Thr Asn Phe Ala Gln Lys Phe 0 55 60
ln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ser Tyr 5 70 75 80
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la Ser Leu Asn Trp Gly Tyr Trp Gly Arg Gly Thr Leu Val Thr Val 00 105 110
er Ser
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hr Val Thr Ile Ser Cys Thr Gly Ser Ser Gly Ser Ile Ala Ser Asn 0 25 30
yr Val Gln Trp Tyr Gln Gln Arg Pro Asp Ser Ala Pro Thr Thr Val 5 40 45

Ile Tyr Glu Asp Asn Arg Arg Ser Ser Gly Val Pro Asp Arg Phe Ser 50 55 60 Gly Ser Ile Asp Ser Asn Ser Ala Ser Leu Ser Ile Ser Gly Leu Lys 75 65 70 80 Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser Gly 85 90 95 His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ala 100 105 110 <210> SEQ ID NO 29 <211> LENGTH: 120 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 29 Glu Val Gln Leu Val Glu Ser Gly Glu Gly Leu Val Lys Pro Gly Gly 10 5 Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Arg Ser Tyr 20 Ser Leu Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val 35 40 45 Ser Ser Ile Ser Ser Thr Ser Thr Tyr Ile Tyr Tyr Ala Asp Ser Val 55 50 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ala Lys Asn Thr Leu Tyr 65 70 75 80 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys 90 85 95 Val Arg Leu Gly Ser Gly Gly Gly Tyr Phe Pro Asp Tyr Trp Gly Arg 100 105 110 Gly Thr Leu Val Thr Val Ser Ser 115 120 <210> SEQ ID NO 30 <211> LENGTH: 110 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 30 Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln 1 5 10 15 Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala 30 20 25 Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr 35 40 45 Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser 50 55 60 Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu 70 65 75 80 Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His

85 90 95 Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ala 100 105 110 <210> SEQ ID NO 31 <211> LENGTH: 114 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 31 Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 5 10 15 1 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr 20 25 30 Ala Met Ser Trp Ala Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 Ser Ser Ile Ser Gly Asp Gly Gly Arg Ile Leu Asp Ala Asp Ser Ala 50 55 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 70 65 75 Leu Gln Met Asn Gly Leu Arg Val Glu Asp Thr Ala Leu Tyr Tyr Cys 90 95 85 Ala Arg Ala Asp Gly Asn Tyr Trp Gly Arg Gly Thr Met Val Thr Val 100 105 110 Ser Ser <210> SEQ ID NO 32 <211> LENGTH: 112 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 32 Gln Ser Val Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln 1 5 10 15 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr 20 25 30 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu 40 45 35 Met Ile Tyr Glu Gly Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe 55 50 60 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu 70 75 65 80 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Thr Arg 85 90 95 Ser Thr Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ala 100 105 110 <210> SEQ ID NO 33

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Ser Leu Lys Ile Ser Cys Gln Gly Ser Gly Tyr Arg Phe Ser Ser Asp 20 25 30 Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met 35 40 45 Gly Ile Val Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe 50 55 60 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr 70 75 65 80 Leu Gln Trp Ser Gly Leu Lys Ala Ser Asp Thr Ala Lys Tyr Tyr Cys 85 90 95 Ala Arg Val Gln Gln Ala Val Gly Ala Lys Gly Tyr Ala Met Asp Val 105 100 110 Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser 115 120 <210> SEQ ID NO 38 <211> LENGTH: 112 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 38 Gln Thr Val Val Ile Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly 5 10 1 15 Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser 20 25 30 Tyr Tyr Pro Ser Trp Tyr Arg Gln Thr Pro Gly Gln Ala Pro His Thr 35 40 45 Leu Ile His Asn Thr Lys Ile Arg Ser Ser Gly Val Pro Asp Arg Phe 50 55 60 Ser Gly Ser Ile Leu Gly Asn Asn Ala Ala Leu Thr Ile Thr Gly Ala 75 65 70 80 Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Ser 85 90 95 Gly Ile Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ala 100 105 110 <210> SEQ ID NO 39 <211> LENGTH: 122 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 39 Gln Val Gln Leu Gln Glu Ser Gly Ala Gly Leu Val Lys Pro Ser Gly 1 10 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Gly 20 25 30 Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp 35 40 45 Ile Gly Glu Ile Ser His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser Leu Asn Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg Val Arg Gly Thr Val Gly Asp Thr Arg Gly Pro Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser <210> SEQ ID NO 40 <211> LENGTH: 110 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 40 Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly As<br/>n Thr Ala Ser Leu Thr Ile Thr Gly Ala Gl<br/>n Ala Glu $% \mathbb{C}$ Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ala <210> SEO ID NO 41 <211> LENGTH: 124 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 41 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Arg Val Ser Cys Lys Gly Ser Gly Asn Thr Phe Thr Gly His Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Leu Gly Trp Ile Asp Pro Asn Thr Gly Asp Ile Gln Tyr Ser Glu Asn Phe Lys Gly Ser Val Thr Leu Thr Arg Asp Pro Ser Ile As<br/>n Ser Val Phe Met Asp Leu Ile Arg Leu Thr Ser Asp Asp Thr Ala Met Tyr Tyr Cys 

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Ala Arg Glu Gly Ala Gly Leu Ala Asn Tyr Tyr Tyr Tyr Gly Leu Asp 105 100 110 Val Trp Gly Arg Gly Thr Met Val Thr Val Ser Ser 115 120 <210> SEQ ID NO 42 <211> LENGTH: 111 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 42 Gln Thr Val Val Leu Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly 5 1 10 15 Thr Val Thr Leu Thr Cys Gly Leu Asn Phe Gly Ser Val Ser Thr Ala 30 20 25 Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr 35 40 45 Leu Ile Tyr Gly Thr Asn Ile Arg Ser Ser Gly Val Pro Asp Arg Phe 50 55 60 Ser Gly Ser Ile Val Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala 70 65 75 80 Gln Thr Glu Asp Glu Ser Asp Tyr Tyr Cys Ala Leu Tyr Met Gly Ser 90 85 95 Gly Met Leu Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Ala 100 105 110 <210> SEQ ID NO 43 <211> LENGTH: 123 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 43 Glu Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg 5 10 1 15 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr 20 25 30 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 40 45 35 Ala Val Ile Ser Tyr Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val 55 50 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 75 65 70 80 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Arg Thr Gly Glu Tyr Ser Gly Tyr Asp Thr Ser Gly Tyr Ser Asn 100 105 110 Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser 120 115

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Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe 50 55 60 Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala 75 65 70 80 Gln Ala Asp Asp Glu Ser Asn Tyr Tyr Cys Met Leu Tyr Met Gly Ser 85 90 95 Gly Met Tyr Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Ala 100 105 110 <210> SEQ ID NO 51 <211> LENGTH: 120 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 51 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 10 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr 25 20 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val 50 55 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 70 75 65 80 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 90 85 95 Ala Arg Val Ser Gly Ser His Phe Pro Phe Phe Asp Ser Trp Gly Gln 105 100 110 Gly Thr Met Val Thr Val Ser Ser 115 120 <210> SEQ ID NO 52 <211> LENGTH: 110 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 52 Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln 1 5 10 15 Thr Ala Arg Ile Thr Cys Gly Gly Asp Lys Ile Gly His Lys Ser Val 25 20 30 His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Leu Val Tyr 35 40 45 Asp Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser 50 55 60 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly 75 65 70 80 Asp Glu Ala Ala Tyr His Cys Gln Val Trp Asp Arg Ser Ser Asp Pro

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20			25					30						
Ala Met Se 35	r Trp	Val	Arg 40	Gln	Ala	Pro	Gly	Lys 45	Gly	Leu	Glu	Trp	Val	
Ser Ala Il 50	e Ser	Gly	Ser 55	Gly	Gly	Ser	Thr	Tyr 60	Tyr	Ala	Asp	Ser	Val	
Lys Gly Ar 65	g Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	ГЛа	Asn	Thr	Leu	Tyr 80	î
Leu Gln Me 85	t Asn	Ser	Leu 90	Arg	Ala	Glu	Asp	Thr 95	Ala	Val	Tyr	Tyr	Суз	3
Ala Arg Gl 100	y Gly	Ser	Gly 105	Ser	Asp	Tyr	Trp	Gly 110	Gln	Gly	Thr	Met	Val	
Thr Val Se 115	r Ser													
-	TH: 1 : PRT NISM: JRE: /KEY: R INF hetic	10 Art: sou: ORMA poly	rce FION:	: /nc	-		cript	ion	of A	Artii	ficia	al Se	equer	nce:
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1 Thr Val Th 20	r Ile	5 Ser	Суз 25	Thr	Arg	Ser	10 Ser	Gly 30	Tyr	Ile	Asp	15 Ser	Lys	3
Tyr Val Gl: 35	n Trp	Tyr		Gln	Arg	Pro	Gly		Ala	Pro	Thr	Thr	Val	
Ile Tyr Gl 50	u Asp	Asn	Arg 55	Arg	Pro	Ser	Gly	Val 60	Pro	Asp	Arg	Phe	Ser	:
Gly Ser Il 65	e Asp	Ser	Asn 70	Ser	Ala	Ser	Leu	Thr 75	Ile	Ser	Gly	Leu	Glu 80	ι
Thr Glu As 85	p Glu	Ala	Asp 90	Tyr	Tyr	Сув	Gln	Ser 95	Tyr	Asp	Asp	Thr	Asn	1
Val Val Ph 100	e Gly	Gly	Gly 105	Thr	Lys	Val	Thr	Val 110	Leu	Gly	Ala			
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Ser Val Ly 20	s Val	Ser	Суз 25	ГЛа	Ala	Ser	Gly	Tyr 30	Asp	Phe	Ser	Asn	Tyr	;
Gly Phe Se 35	r Trp	Val	Arg 40	Gln	Ala	Pro	Gly	Gln 45	Gly	Leu	Glu	Trp	Met	1
Gly Trp Il 50	e Ser	Ser	Tyr 55	Asn	Gly	Tyr	Thr	Asn 60	Tyr	Ala	Gln	Arg	Leu	L

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr 70 75 65 80 Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Arg Asp Arg Gly Leu Gly Asn Trp Tyr Phe Asp Leu Trp Gly Gln 100 105 110 Gly Thr Leu Val Thr Val Ser Ser 115 120 <210> SEQ ID NO 62 <211> LENGTH: 112 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 62 Gln Ser Val Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln 1 5 10 15 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr 25 20 30 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu 35 40 45 Met Ile Tyr Glu Gly Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe 55 50 60 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu 65 70 75 80 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Thr Arg 95 85 90 Ser Thr Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ala 100 105 110 <210> SEQ ID NO 63 <211> LENGTH: 108 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 63 Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln 5 10 1 15 Thr Ala Arg Met Thr Cys Gly Gly Asn Asn Ile Glu Ser Lys Thr Val 25 20 30 His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr 35 40 45 Asn Asp Asn Val Arg Pro Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser 50 55 60 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Asn Arg Val Glu Ala Gly 70 75 65 Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Arg Asp Gln 85 90 95

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Ile Tyr Asp Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser 50 55 60 Gly Ser Lys Ser Gly Asn Ser Ala Ser Leu Asp Ile Ser Gly Leu Gln 75 65 70 80 Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu 85 90 95 Ser Glu Phe Leu Phe Gly Thr Arg Thr Lys Leu Thr Val Leu 100 105 110 <210> SEQ ID NO 71 <211> LENGTH: 110 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 71 Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Ser Pro Gly Gln 10 Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr 20 30 Asp Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu 35 45 40 Met Ile Tyr Glu Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe 50 55 60 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Val Ser Gly Leu 70 75 65 80 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Gly Ser 85 90 95 Lys Asn Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu 100 105 110 <210> SEO ID NO 72 <211> LENGTH: 111 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 72 Gln Ala Val Leu Thr Gln Pro Ser Ala Val Ser Gly Ala Pro Gly Gln 10 1 5 15 Arg Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asn Ile Gly Thr Asn 20 25 30 Tyr Leu Val His Trp Tyr Gln Gln Arg Pro Gly Thr Ala Pro Gln Leu 40 35 45 Leu Val Ser Gly Asn Asn Thr Arg Pro Ser Gly Val Thr Asp Arg Phe 50 55 60 Ser Val Ser Lys Ser Ala Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu 70 75 80 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Asp Ile Asn 85 90 95 Leu Arg Val Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu

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Tyr Val Tyr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu 35 40 45 Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser 50 55 60 Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg 65 70 75 80 Ser Glu Asp Glu Thr Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu 85 90 95 Ser Gly Arg Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu 100 105 110 <210> SEQ ID NO 78 <211> LENGTH: 109 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 78 Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys 5 10 1 Thr Val Thr Ile Ser Cys Thr Gly Ser Ser Gly Ser Ile Ala Ser Asn 20 25 30 Tyr Val Gln Trp Tyr Gln Gln Arg Pro Asp Ser Ala Pro Thr Thr Val 35 40 45 Ile Tyr Glu Asp Asn Arg Arg Ser Ser Gly Val Pro Asp Arg Phe Ser 55 50 60 Gly Ser Ile Asp Ser Asn Ser Ala Ser Leu Ser Ile Ser Gly Leu Lys 70 75 65 80 Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser Gly 85 90 95 His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu 100 105 <210> SEQ ID NO 79 <211> LENGTH: 108 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 79 Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln 1 5 10 15 Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala 20 25 30 Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr 35 40 45 Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser 50 55 60 Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu 70 65 75 80 Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His

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0 55 60 er Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Arg Ala 5 70 70 75 80 Clu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Ser Arg Leu Ser 90 90 95 er Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu 105 210> SEQ ID NO 92 211> LENGTH: 108 212> TYPE: PRT 213> ORGANISM: Artificial Sequence 220> FEATURE:
5 70 75 80 Flu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Asp Ser Arg Leu Ser 5 90 95 er Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu 00 105 210> SEQ ID NO 92 211> LENGTH: 108 212> TYPE: PRT 213> ORGANISM: Artificial Sequence 220> FEATURE:
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hr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala 0 25 30
er Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr 5 40 45
ly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser 0 55 60
er Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu 5 70 75 80
sp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His 5 90 95
al Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu 00 105
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rg Val Thr Ile Ser Cys Ser Gly Ser Ser Asn Ile Gly Ser Asn 0 25 30
er Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
5   40   45

-	С	on	t	l	n	u	е	d

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Asp Ala Ser Leu Asn Thr Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu <210> SEQ ID NO 94 <211> LENGTH: 108 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 94 Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Gly Ser Pro Gly Lys Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Tyr Ile Asp Ser Lys Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ala Pro Thr Thr Val Ile Tyr Glu Asp Asn Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Ile Asp Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly Leu Glu Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Asp Thr Asn Val Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu <210> SEQ ID NO 95 <211> LENGTH: 110 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEOUENCE: 95 Gln Ser Val Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu 

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ccagggaagg ggctggagtg ggtttcatac attagtagtt ctggtaatac catattctac	180
gcagactotg tgaagggoog attoaccato tocagagaca gtgocaagaa ttoagtgtot	240
ctgcagatga acageetgag agaegaggae aeggetgtgt attaetgtge tteetaetae	300
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Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser	

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35					40					45					
Gln 50	Asp	Val	Asn	Thr	Ala 55	Val	Ala	Trp	Tyr	Gln 60	Gln	Lys	Pro	Gly	Lys
Ala 65	Pro	Гла	Leu	Leu	Ile 70	Tyr	Ser	Ala	Ser	Phe 75	Leu	Tyr	Ser	Gly	Val 80
Pro 85	Ser	Arg	Phe	Ser	Gly 90	Ser	Arg	Ser	Gly	Thr 95	Asp	Phe	Thr	Leu	Thr
Ile 100	Ser	Ser	Leu	Gln	Pro 105	Glu	Asp	Phe	Ala	Thr 110	Tyr	Tyr	Сүз	Gln	Gln
His 115	Tyr	Thr	Thr	Pro	Pro 120	Thr	Phe	Gly	Gln	Gly 125	Thr	Lys	Val	Glu	Ile
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Gly 145	Ser	Gly	Gly	Gly	Gly 150	Ser	Glu	Val	Gln	Leu 155	Val	Glu	Ser	Gly	Gly 160
Gly 165	Leu	Val	Gln	Pro	Gly 170	Gly	Ser	Leu	Arg	Leu 175	Ser	Сүз	Ala	Ala	Ser
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Thr 210	Arg	Tyr	Ala	Asp	Ser 215	Val	Lys	Gly	Arg	Phe 220	Thr	Ile	Ser	Ala	Aab
Thr 225	Ser	Lys	Asn	Thr	Ala 230	Tyr	Leu	Gln	Met	Asn 235	Ser	Leu	Arg	Ala	Glu 240
Asp 245	Thr	Ala	Val	Tyr	Tyr 250	Суз	Ser	Arg	Trp	Gly 255	Gly	Asp	Gly	Phe	Tyr
Ala 260	Met	Asp	Tyr	Trp	Gly 265	Gln	Gly	Thr	Leu	Val 270	Thr	Val	Ser	Ser	Aab
Gln 275	Glu	Pro	Lys	Ser	Cys 280	Asp	Lys	Thr	His	Thr 285	Ser	Pro	Pro	Cys	Ser
Ala 290	Pro	Glu	Leu	Leu	Gly 295	Gly	Pro	Ser	Val	Phe 300	Leu	Phe	Pro	Pro	Lys
Pro 305	Lys	Asp	Thr	Leu	Met 310	Ile	Ser	Arg	Thr	Pro 315	Glu	Val	Thr	Cys	Val 320
Val 325	Val	Asp	Val	Ser	His 330		Asp	Pro		Val 335	Lys	Phe	Asn	Trp	Tyr
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	Tyr	Asn	Ser	Thr	Tyr 360	Arg	Val	Val	Ser		Leu	Thr	Val	Leu	His
	Asp	Trp	Leu	Asn	Gly 375	-	Glu	Tyr	Lys		Lys	Val	Ser	Asn	Lys
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	Arg	Glu	Pro	Gln	Val 410	Tyr	Thr	Leu	Pro		Ser	Arg	Asp	Glu	
	Lys	Asn	Gln	Val	Ser 425	Leu	Thr	Суз	Leu		Гла	Gly	Phe	Tyr	Pro
	Asp	Ile	Ala	Val	Glu 440	Trp	Glu	Ser	Asn		Gln	Pro	Glu	Asn	Asn
CCF										773					

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Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu 450 455 460 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val 465 470 475 480 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln 485 490 495 Lys Ser Leu Ser Leu Ser Pro Gly Lys 500 505 <210> SEQ ID NO 160 <211> LENGTH: 66 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticoligonucleotide" <400> SEQUENCE: 160 atggattttc aagtgcagat tttcagcttc ctgctaatca gtgcttcagt cataatgtcc 60 agagga 66 <210> SEQ ID NO 161 <211> LENGTH: 22 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpeptide" <400> SEQUENCE: 161 Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser 1 5 10 15 Val Ile Met Ser Arg Gly 20 <210> SEQ ID NO 162 <211> LENGTH: 327 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolynucleotide" <400> SEQUENCE: 162 gatattcaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60 attacctgcc gcgcgagcca ggatgtgaac accgcggtgg cgtggtatca gcagaaaccg 120 ggcaaagcgc cgaaactgct gatttatagc gcgagctttc tgtatagcgg cgtgccgagc 180 cgctttagcg gcagccgcag cggcaccgat tttaccctga ccattagcag cctgcagccg 240 gaagattttg cgacctatta ttgccagcag cattatacca ccccgccgac ctttggccag 300 ggcaccaaag tggaaattaa acgcacc 327 <210> SEQ ID NO 163 <211> LENGTH: 109

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ctgraphing i gaaageeg ettaecat agegegat ceageamaa cacegett 240 ctgraphing acageetge geogamgat accgegigt attatige geochggge 200 geogataget titatigeat geatating geochggge eccipage egtage age age age age age age age age age	-continued	
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2410. SEC ID NO 167         2111. LENGTH: 120         2120. TYPE: PRT         2120. SEC ID: NO 167         2121. SUBME/ET: Source         2220. SEC ID: NO 167         2310. SUBME/ET: Source         2321. SUBME/ET: Source         2322. SOURCE: 167         310. Val Gin Leu Val Giu Ser Giy Giy Giy Leu Val Gin Pro Giy Giy         1       5         20       15         21       10         21       15         20       14         21       10         21       10         21       10         21       10         21       10         21       10         21       10         21       10         21       10         21       10         21       10         21       10         21       10         21       10         21       10         21	gcggatagcg tgaaaggccg ctttaccatt agcgcggata ccagcaaaaa caccgcgtat 240	
<pre>210. 580 DB %0 147</pre>	ctgcagatga acageetgeg egeggaagat acegeggtgt attattgeag eegetgggge 300	
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Glu Val Glu Leu Val Glu Ser Gly Gly Gly Leu Val Glu Pro Gly Gly 1 5 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asm Ile Lys Asp Thr 20 25 Tyr Ile His Trp Val Arg Glu Ala Pro Gly Lys Gly Leu Glu Trp Val 40 45 Ala Arg Ile Tyr Pro Thr Asm Gly Tyr Thr Arg Tyr Ala Asp Ser Val 50 So Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asm Thr Ala Tyr 60 Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asm Thr Ala Tyr 60 Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asm Thr Ala Tyr 75 80 Ser Arg Trp Gly Gly App Gly Phe Tyr Ala Wet Asp Tyr Trp Gly Gln 10 10 10 210 520 TO NO 168 2110 LENNTH: 45 2120 TPE: NNA 2130 ORGANISM: Artificial Sequence 2200 FEATURE: 2205 SEQ ID NO 168 2323 OTHER INFORMATION: /note="Description of Artificial Sequence: 397theticoligonucleotide" 2400 SEQUENCE: 168 393gerccaast cttgtgacaa aactcacaca tctccaccgt gctca 240 2410 SEQ ID NO 169 24210 SEQ ID NO 169 24210 SEQ ID NO 169 24210 SEQ DIN 169 24210 SEQ UD NO 169 24210 SEQ UD NO 169 24210 SEQUENCE: 164 393 OTHER INFORMATION: /note="Description of Artificial Sequence: 397theticoligonucleotide" 2400 SEQUENCE: 164 303 OTHER INFORMATION: /note="Description of Artificial Sequence: 2400 SEQUENCE: 169 301 Chrono Sequence: 169 302 OTHER INFORMATION: /note="Description of Artificial Sequence: 397theticoligonucleotide" 2030 OTHER INFORMATION: /note="Description of Artificial Sequence: 397theticoligonucleotide" 2040 SEQUENCE: 169 301 Leuno Sequence: 169 302 OTHER INFORMATION: /note="Description of Artificial Sequence: 397theticoligonucleotide" 2040 SEQUENCE: 169 301 Leuno Sequence: 169 302 OTHER INFORMATION: /note="Description of Artificial Sequence: 397theticoligonucleotide" 400 SEQUENCE: 169 303 OTHER INFORMATION: /note="Description of Artificial Sequence: 397theticoligonucleotide" 400 SEQUENCE: 169 400 SEQUENCE: 169 4	<210> SEQ ID NO 167 <211> LENGTH: 120 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide"	
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35       40       45         Ala Arg Ile Tyr Pro Thr Am Gly Tyr Thr Arg Tyr Ala Asp Ser Val 50       60         50       55       60         50       55       60         50       55       60         50       55       60         55       70       75         66       75       80         55       70       75         66       75       80         55       70       75         70       75       80         55       90       95         55       90       95         56       77       77         70       100       105         100       105       110         110       110       110         110       110       110         110       110       110         110       110       110         111       120       110         2120       TPK       110         2120       TPK       110         2120       TPK       120         2212       TPK       120         220       FRATCHY	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr 20 25 30	
50 55 55 60 50 55 70 50 50 50 50 50 50 50 50 50 50 50 50 50	Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45	
<pre>c5 70 70 75 80 So 70 75 80 So 70 90 So 75 9</pre>	Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val 50 55 60	
<pre>85 90 95 Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln 100 105 110 100 105 110 100 Cly Thr Leu Val Thr Val Ser Ser 115 120 </pre>	Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr 65 70 75 80	
100 1 105 1 107 107 107 107 107 107 107 107 107 1	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95	
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Ser Ser Ser Phe Thr Val Asn Trp Leu Arg Gln Ala Pro Gly Gln Gly 50 55 60
Leu Glu Trp Met Gly Gly Ile Thr Pro Met Phe Gly Thr Ala Asn Tyr 65 70 75 80
Ala Gln Met Phe Glu Asp Arg Val Thr Ile Thr Ala Asp Glu Met Glu 85 90 95
Leu Ser Gly Leu Thr Ser Glu Asp Thr Ala Val Tyr Phe Cys Ala Thr 100 105 110
Gly Pro Ser Asp Tyr Val Trp Gly Ser Tyr Arg Phe Leu Asp Thr Trp 115 120 125
Gly Arg Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly 130 135 140
Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ala Val Leu Thr Gln 145 150 155 160
Pro Ser Ser Val Ser Ala Ala Pro Gly Gln Glu Val Ser Ile Ser Cys 165 170 175
Ser Gly Ala Arg Ser Asn Val Gly Gly Asn Tyr Val Ser Trp Tyr Gln 180 185 190
His Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Asp Asn Asn Lys 195 200 205
Arg Pro Ser Gly Met Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr 210 215 220
Ser Ala Thr Leu Gly Ile Thr Gly Val Gln Thr Glu Asp Glu Ala Asp         225       230       235       240
Tyr Tyr Cys Ala Thr Trp Asp Ser Ser Leu Ser Ala Val Val Phe Gly 245 250 255
Gly Gly Thr Lys Leu Thr Val Leu Gly Asp Val Arg Glu Pro Lys Ser         260       265         270
Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu 275 280 285
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu         290       295         300
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser 305 310 315 320
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu 325 330 335
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Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

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Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val 420
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro 435 440 445
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr 450 455 460
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Gly Gly Thr Lys Val Thr Val Leu Gly Asp Val Arg Glu Pro Lys Ser 260 265 270	
Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu 275 280 285	
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu 290 295 300	
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Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr 340 345 350	
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn 355 360 365	
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro 370 375 380	
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln 385 390 395 400	
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Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val 420 425 430	
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro 435 440 445	
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr 450 455 460	
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cgagaaccac aggtgtac	ac cctgccccca tcccgggatg agctgaccaa gaaccaggtc	1260
ageetgaeet geetggte	aa aggettetat eeaagegaca tegeegtgga gtgggagage	1320
aatgggcagc cggagaac	aa ctacaagacc acgcctcccg tgctggactc cgacggctcc	1380
ttetteetet acageaag	ct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc	1440
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Lys Pro Gly Ala Ser 35	Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser 40 45	
Phe Thr Ala Phe Tyr 50	Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly 55 60	
Leu Glu Tyr Leu Gly 65	Trp Ile Asp Pro Asn Thr Gly Ala Thr Lys Tyr 70 75 80	
Ala Gln Arg Phe Glr 85	Gly Arg Val Ile Met Thr Trp Asp Thr Ser Ile 90 95	
Thr Thr Ala Thr Met 100	Glu Leu Ser Arg Leu Thr Ser Asp Asp Ser Ala 105 110	
Val Tyr Tyr Cys Val 115	Arg Asp Leu Arg Glu Trp Gly Tyr Glu Leu Ser 120 125	
Val Glu Tyr Trp Gly 130	Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly 135 140	

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Gly 145	Gly	Ser	Gly	Gly	Gly 150	Gly	Ser	Gly	Gly	Gly 155	Gly	Ser	Ala	Gln	Ser 160							
Val 165	Leu	Thr	Gln	Pro	Pro 170	Ser	Ala	Ser	Gly	Thr 175	Pro	Gly	Gln	Arg	Val							
Thr 180	Ile	Ser	Cys	Ser	Gly 185	Ser	Ser	Ser	Asn	Ile 190	Gly	Ser	Asn	Tyr	Val							
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Arg 210	Asn	Asn	Gln	Arg	Pro 215	Ser	Gly	Val	Pro	Asp 220	Arg	Phe	Ser	Gly	Ser							
Lys 225	Ser	Gly	Thr	Ser	Ala 230	Ser	Leu	Ala	Ile	Ser 235	Gly	Leu	Arg	Ser	Glu 240							
Asp 245	Glu	Ala	Asp	Tyr	Tyr 250	Суз	Ala	Ala	Trp	Asp 255	Asp	Ser	Leu	Ser	Gly							
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Glu 275	Pro	Lys	Ser	Ser	Asp 280	Гла	Thr	His	Thr	Cys 285	Pro	Pro	Сүз	Pro	Ala							
Pro 290	Glu	Leu	Leu	Gly	Gly 295	Pro	Ser	Val	Phe	Leu 300	Phe	Pro	Pro	Lys	Pro							
Lys 305	Aab	Thr	Leu	Met	Ile 310	Ser	Arg	Thr	Pro	Glu 315	Val	Thr	Суз	Val	Val 320							
Val 325	Aab	Val	Ser	His	Glu 330	Asp	Pro	Glu	Val	Lys 335	Phe	Asn	Trp	Tyr	Val							
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Asp 370	Trp	Leu	Asn	Gly	Lys 375	Glu	Tyr	Гла	Суа	Lys 380	Val	Ser	Asn	ГЛа	Ala							
Leu 385	Pro	Ala	Pro	Ile	Glu 390	ГЛа	Thr	Ile	Ser	Lys 395	Ala	Lys	Gly	Gln	Pro 400							
Arg 405	Glu	Pro	Gln	Val	Tyr 410	Thr	Leu	Pro	Pro	Ser 415	Arg	Asp	Glu	Leu	Thr							
Lys 420	Asn	Gln	Val	Ser	Leu 425	Thr	Суз	Leu	Val	Lys 430	Gly	Phe	Tyr	Pro	Ser							
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		Ser	Leu	Ser	Pro	Gly	Lys															
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Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr	

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35															
					40					45					
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Ser 100	Thr	Ala	Tyr	Met	Glu 105	Leu	Ser	Arg	Leu	Arg 110	Ser	Asp	Asp	Thr	Ala
Val 115	Tyr	Tyr	Сув	Ala	Arg 120	Asp	Ser	Thr	Met	Ala 125	Pro	Gly	Ala	Phe	Asp
Ile 130	Trp	Gly	Arg	Gly	Thr 135	Leu	Val	Thr	Val	Ser 140	Ser	Gly	Gly	Gly	Gly
Ser 145	Gly	Gly	Gly	Gly	Ser 150	Gly	Gly	Gly	Gly	Ser 155	Ala	Gln	Ser	Val	Leu 160
Thr 165	Gln	Pro	Pro	Ser	Val 170	Ser	Val	Ala	Pro	Gly 175	Gln	Thr	Ala	Arg	Met
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Thr 225	Ala	Thr	Leu	Thr	Ile 230	Asn	Arg	Val	Glu	Ala 235	Gly	Asp	Glu	Ala	Asp 240
Tyr 245	Tyr	Суз	Gln	Val	Trp 250	Asp	Ser	Ser	Arg	Asp 255	Gln	Gly	Val	Phe	Gly
Gly 260	Gly	Thr	Lys	Leu	Thr 265	Val	Leu	Gly	Asp	Val 270	Arg	Glu	Pro	Lys	Ser
Ser 275	Asp	Lys	Thr	His	Thr 280	Суз	Pro	Pro	Суз	Pro 285	Ala	Pro	Glu	Leu	Leu
Gly 290	Gly	Pro	Ser	Val	Phe 295	Leu	Phe	Pro	Pro	Lys 300	Pro	Lys	Asp	Thr	Leu
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His 325	Glu	Asp	Pro	Glu	Val 330	Lys	Phe	Asn	Trp	Tyr 335	Val	Asp	Gly	Val	Glu
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Ile 385	Glu	Lys	Thr	Ile	Ser 390	Lys	Ala	Lys	Gly	Gln 395	Pro	Arg	Glu	Pro	Gln 400
Val 405	Tyr	Thr	Leu	Pro	Pro 410	Ser	Arg	Asp	Glu	Leu 415	Thr	Lys	Asn	Gln	Val
Ser 420	Leu	Thr	Cys	Leu		Lys	Gly	Phe	Tyr		Ser	Asp	Ile	Ala	Val
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Met His Clu Ala Leu His An His Tyr Thr Cln Lys Ser Leu Ser Leu Ser Pro Cly Lys 500 callos SEO TD NO 182 callos SEO TO NO 182 callos SEO TE NO 182 callos SEO TE SEO TO NO 182	Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
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tacagcaagc	tcacc	gtgga	caaga	gcagg	tgg	gcagc	agg	ggaa	acgtc	tt (	ctcat	getee	1440	
gtgatgcatg	aggct	ctgca	caacca	actac	aco	gcaga	aga	gcct	ctcc	ct 🤅	gtcto	cgggt	1500	
aaatga													1506	
-	IH: 50 PRT NISM: J JRE: /KEY: s R INFO heticp	1 Artif: source RMATI( olype]	e DN:/no	-		ript	ion	of A	rtif:	icia	al Se	quence:		
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Met Glu Al 1		Ala G. 5	In Leu	Leu	Pne	Leu 10	Leu	Leu	Leu	Trp	Leu 15	Pro		
7 ml ml.						TO								
Asp Thr Th 20	r Gly	Glu V 2		Leu	Leu	Glu	Ser 30	Gly	Gly	Gly	Leu	Val		
-	-	2	5 eu Arg			Glu Cys	30	-	-	-				
20 Gln Pro Gl	y Gly	2! Ser L 4	5 eu Arg 0 et Ser	Leu	Ser	Glu Cys Arg	30 Ala 45	Ala	Ser	Gly	Phe	Thr		
20 Gln Pro Gl 35 Phe Ser Se	y Gly r Tyr .	2 Ser L 4 Ala M 5	5 eu Arg 0 et Ser 5 la Ile	Leu Trp	Ser Val	Glu Cys Arg Ser	30 Ala 45 Gln 60	Ala Ala	Ser Pro	Gly Gly	Phe Lys	Thr Gly		
20 Gln Pro Gl 35 Phe Ser Se 50 Leu Glu Tr	y Gly r Tyr . p Val	2: Ser L 4 Ala M 5 Ser A 7	5 eu Arg 0 et Ser 5 1a Ile 0 1y Arg	Leu Trp Ser	Ser Val Gly	Glu Cys Arg Ser Ile	30 Ala 45 Gln 60 Gly 75	Ala Ala Gly	Ser Pro Ser	Gly Gly Thr	Phe Lys Tyr	Thr Gly Tyr 80		
20 Gln Pro Gl 35 Phe Ser Se 50 Leu Glu Tr 65 Ala Asp Se	y Gly r Tyr . p Val r Val	2: Ser L 4 Ala M 5 Ser A 7 Lys G 9 Lys G	5 eu Arg 0 et Ser 5 la Ile 0 ly Arg 0	Leu Trp Ser Phe	Ser Val Gly Thr	Glu Cys Arg Ser Ile Leu	30 Ala 45 Gln 60 Gly 75 Ser 95	Ala Ala Gly Arg	Ser Pro Ser Asp	Gly Gly Thr Asn	Phe Lys Tyr Ser	Thr Gly Tyr 80 Lys		

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_	$\sim$	$\sim$	τт	L	_	τ.τ	u	-	u

Trp Gly Arg 130	Gly Thr	Thr 1 135	Val	Thr	Val	Ser	Ser 140	Gly	Gly	Gly	Gly	Ser
Gly Gly Gly 145	Gly Ser	Gly ( 150	Gly	Gly	Gly	Ser	Ala 155	His	Val	Ile	Leu	Thr 160
Gln Pro Pro 165	Ser Thr	Ser ( 170	Gly	Thr	Pro	Gly	Gln 175	Thr	Val	Thr	Ile	Ser
Cys Ser Gly 180	Ser Ser	Ser 2 185	Asn	Ile	Gly	Ser	His 190	Tyr	Val	Tyr	Trp	Tyr
Gln Gln Leu 195	Pro Gly	Thr 2 200	Ala	Pro	Lys	Leu	Leu 205	Ile	Tyr	Arg	Asn	Asn
Gln Arg Pro 210	Ser Gly	Val 1 215	Pro	Asp	Arg	Phe	Ser 220	Gly	Ser	Lys	Ser	Gly
Thr Ser Ala 225	Ser Leu	Ala : 230	Ile	Ser	Gly	Leu	Arg 235	Ser	Glu	Asp	Glu	Thr 240
Asp Tyr Tyr 245	Cys Ala	Ala ' 250	Trp	Asp	Asp	Ser	Leu 255	Ser	Gly	Arg	Val	Phe
Gly Thr Gly 260	Thr Lys	Leu / 265	Thr	Val	Leu	Gly	Asp 270	Val	Arg	Glu	Pro	Lys
Ser Ser Asp 275	Lys Thr	His / 280	Thr	Cys	Pro	Pro	Cys 285	Pro	Ala	Pro	Glu	Leu
Leu Gly Gly 290	Pro Ser	Val 1 295	Phe	Leu	Phe	Pro	Pro 300	Lys	Pro	Lys	Asp	Thr
Leu Met Ile 305	Ser Arg	Thr 1 310	Pro	Glu	Val	Thr	Cys 315	Val	Val	Val	Asp	Val 320
Ser His Glu 325	Asp Pro	Glu 7 330	Val	Lys	Phe	Asn	Trp 335	Tyr	Val	Asp	Gly	Val
Glu Val His 340	Asn Ala	Lys 345	Thr	Lys	Pro	Arg	Glu 350	Glu	Gln	Tyr	Asn	Ser
Thr Tyr Arg 355	Val Val	Ser 7 360	Val	Leu	Thr	Val	Leu 365	His	Gln	Asp	Trp	Leu
Asn Gly Lys 370	Glu Tyr	Lys ( 375	Суз	Гла	Val	Ser	Asn 380	LYa	Ala	Leu	Pro	Ala
Pro Ile Glu 385	Lys Thr	Ile : 390	Ser	Lys	Ala	Lys	Gly 395	Gln	Pro	Arg	Glu	Pro 400
Gln Val Tyr 405	Thr Leu	Pro 1 410	Pro	Ser	Arg	Asp	Glu 415	Leu	Thr	Lys	Asn	Gln
Val Ser Leu 420	Thr Cys	Leu 7 425	Val	Lys	Gly	Phe	Tyr 430	Pro	Ser	Asp	Ile	Ala
Val Glu Trp 435	Glu Ser	Asn ( 440	Gly	Gln	Pro	Glu	Asn 445	Asn	Tyr	Lys	Thr	Thr
Pro Pro Val 450	Leu Asp	Ser 2 455	Asp	Gly	Ser	Phe	Phe 460	Leu	Tyr	Ser	Lys	Leu
Thr Val Asp 465	Lys Ser	Arg / 470	Trp	Gln	Gln	Gly	Asn 475	Val	Phe	Ser	Cys	Ser 480
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gccagcaact atgtgcagtg gtaccagcag cgcccggaca gtgcccccac cactgtgatc	600
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gtoctaggtg acgtacgoga goocaaatot totgacaaaa otoacacatg occacogtgo	840
ccagcacctg aacteetggg tggacegtea gtetteetet teeeceeaaa acceaaggae	900
acceteatga teteceggae eeetgaggte acatgegtgg tggtggaegt gageeaegaa	960
gaccetgagg teaagtteaa etggtaegtg gaeggegtgg aggtgeataa tgeeaagaea	1020
aageegeggg aggageagta caacageaeg taeegtgtgg teagegteet caeegteetg	1080
caccaggact ggctgaatgg caaggagtac aagtgcaagg tetecaacaa ageeeteeca	1140
geceecateg agaaaaccat etecaaagee aaagggeage eeegagaaee acaggtgtae	1200
accetgeece cateceggga tgagetgaee aagaaceagg teageetgae etgeetggte	1260
aaaggettet ateeaagega categeegtg gagtgggaga geaatgggea geeggagaae	1320
aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag	1380
ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat	1440
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Asp Thr Thr Gly Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys 20 25 30	

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Lys 35	Pro	Gly	Ser	Ser	Val 40	Lys	Val	Ser	Cys	Lys 45	Ala	Ser	Gly	Gly	Thr
Ile 50	Ser	Asn	Tyr	Ala	Ile 55	Ser	Trp	Val	Arg	Leu 60	Ala	Pro	Gly	Gln	Gly
Leu 65	Glu	Trp	Met	Gly	Ser 70	Ile	Val	Pro	Leu	His 75	Gly	Thr	Thr	Asn	Phe 80
Ala 85	Gln	Lys	Phe	Gln	Gly 90	Arg	Val	Thr	Ile	Thr 95	Ala	Asp	Glu	Ser	Thr
Ser 100	Thr	Ser	Tyr	Met	Glu 105	Val	Asn	Val	Leu	Thr 110	Tyr	Glu	Asp	Thr	Ala
Met 115	Tyr	Tyr	Суз	Ala	Ser 120	Leu	Asn	Trp	Gly	Tyr 125	Trp	Gly	Arg	Gly	Thr
Leu 130	Val	Thr	Val	Ser	Ser 135	Gly	Gly	Gly	Gly	Ser 140	Gly	Gly	Gly	Gly	Ser
Gly 145	Gly	Gly	Gly	Ser	Ala 150	Leu	Asn	Phe	Met	Leu 155	Thr	Gln	Pro	His	Ser 160
Val 165	Ser	Glu	Ser	Pro	Gly 170	Lys	Thr	Val	Thr	Ile 175	Ser	Суз	Thr	Gly	Ser
Ser 180	Gly	Ser	Ile	Ala	Ser 185	Asn	Tyr	Val	Gln	Trp 190	Tyr	Gln	Gln	Arg	Pro
Asp 195	Ser	Ala	Pro	Thr	Thr 200	Val	Ile	Tyr	Glu	Asp 205	Asn	Arg	Arg	Ser	Ser
Gly 210	Val	Pro	Asp	Arg	Phe 215	Ser	Gly	Ser	Ile	Asp 220	Ser	Ser	Ser	Asn	Ser
Ala 225	Ser	Leu	Ser	Ile	Ser 230	Gly	Leu	Lys	Thr	Glu 235	Asp	Glu	Ala	Asp	Tyr 240
Tyr 245	Cys	Gln	Ser	Tyr	Asp 250	Ser	Ser	Gly	His	Val 255	Val	Phe	Gly	Gly	Gly
Thr 260	Lys	Leu	Thr	Val	Leu 265	Gly	Asp	Val	Arg	Glu 270	Pro	Lys	Ser	Ser	Asp
Lys 275	Thr	His	Thr	Сүз	Pro 280	Pro	Cys	Pro	Ala	Pro 285	Glu	Leu	Leu	Gly	Gly
Pro 290	Ser	Val	Phe	Leu	Phe 295	Pro	Pro	Lys	Pro	Lys 300	Asp	Thr	Leu	Met	Ile
Ser 305	Arg	Thr	Pro	Glu	Val 310	Thr	Сув	Val	Val	Val 315	Asp	Val	Ser	His	Glu 320
Asp 325	Pro	Glu	Val	Lys	Phe 330	Asn	Trp	Tyr	Val	Asp 335	Gly	Val	Glu	Val	His
Asn 340	Ala	Lys	Thr	Lys	Pro 345	Arg	Glu	Glu	Gln	Tyr 350	Asn	Ser	Thr	Tyr	Arg
Val 355	Val	Ser	Val	Leu	Thr 360	Val	Leu	His	Gln	Asp 365	Trp	Leu	Asn	Gly	ГЛа
Glu 370	Tyr	Lys	Сүз	Lys	Val 375	Ser	Asn	Lys	Ala	Leu 380	Pro	Ala	Pro	Ile	Glu
Lys 385	Thr	Ile	Ser	Lys	Ala 390	Lys	Gly	Gln	Pro	Arg 395	Glu	Pro	Gln	Val	Tyr 400
Thr 405	Leu	Pro	Pro	Ser	Arg 410	Asp	Glu	Leu	Thr	Lys 415	Asn	Gln	Val	Ser	Leu
Thr 420	Суз	Leu	Val	Lys	Gly 425	Phe	Tyr	Pro	Ser	Asp 430	Ile	Ala	Val	Glu	Trp

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Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp 450 455 460	
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teetgtaagg gttttggata caattttege agegeetgga teggetgggt gegeeagatg	180
cccggcaaag gcctggagtg gatgggggtc atctatcctg gtgactctga tgtcagatac	240
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ctgcagtgga gcagcctgaa agcctcggac accgccatgt attattgtac gagacccgta	360
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cageegeect cagegtetgg gaeeeegga cagagggtea ceatetettg ttetggaage	540
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tecaactetg geaceteage etceetggee ateagtggge teeggteega ggatgagget	720
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gccctcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca	1200
caggtgtaca ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc	1260
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ccggagaaca actacaagac cacgeeteec gtgetggaet ccgacggete ettetteete	1380
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc	1440
gtgatgcatg aggetetgca caaccactac acgeagaaga geeteteeet gteteegggt	1500
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aaatga

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Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Phe Gly Tyr Asn 35 40 45								
Phe Arg Ser Ala Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly 50 55 60								
Leu Glu Trp Met Gly Val Ile Tyr Pro Gly Asp Ser Asp Val Arg Tyr 65 70 75 80								
Ser Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile 85 90 95								
Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala 100 105 110								
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Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln Arg Val Thr Ile Ser 165 170 175								
Cys Ser Gly Ser Ser Asn Ile Gly Thr Asn Thr Val Asn Trp Tyr 180 185 190								
Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Thr Ser Asn 195 200 205								
Gln Arg Pro Ser Gly Val Pro Ala Arg Phe Ser Ala Ser Asn Ser Gly 210 215 220								
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Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Asp Val Arg Glu Pro Lys 260 265 270								
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Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr290295300								
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ln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr 5 40 45	
he Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly 0 55 60	
eu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr 5 70 75 80	
la Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys 5 90 95	
sn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala 00 105 110	
al Tyr Tyr Cys Ala Arg Gln Ser Gly Ala Asp Trp Tyr Phe Asp Leu 15 120 125	
rp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser 30 135 140	
ly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ala Val Leu Thr 45 150 155 160	
ln Pro Ser Ala Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser 65 170 175	
ys Thr Gly Thr Ser Ser Asn Ile Gly Thr Asn Tyr Leu Val His Trp 80 185 190	
yr Gln Gln Arg Pro Gly Thr Ala Pro Gln Leu Leu Val Ser Gly Asn	
95 200 205	

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Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu 275 280 285								
Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp 290 295 300								
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp								
305     310     315     320       Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly								
325 330 335 Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn								
340     345     350       Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp								
355 360 365 Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro								
370 375 380								
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Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys 450 455 460								
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys 465 470 475 480								
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Ser Leu Ser Pro Gly Lys 500								
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Gln Pro Gly Gly Ser Leu 35	Ser Leu Ser Cys Ala Ala Ser ( 45	Gly Phe Thr					
Phe Ser Ser Tyr Gly Met 50 55	Gln Trp Val Arg Gln Ala Pro ( 60	Gly Lys Gly					
Leu Glu Trp Val Ala Phe 55 70	Ile Arg Tyr Asp Gly Ser Ser ( 75	Glu Tyr Tyr 80					
Ala Asp Ser Val Lys Gly 35 90	Arg Phe Thr Ile Ser Arg Asp A 95	Asn Ser Lys					
Asn Thr Leu Tyr Leu Gln 100 105	Met Asn Ser Leu Arg Ala Glu A 110	Asp Thr Ala					
	Thr Leu Glu Ser Ser Leu Trp (	Gly Lys Gly					

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Thr 130	Leu	Val	Thr	Val	Ser 135	Ser	Gly	Gly	Gly	Gly 140	Ser	Gly	Gly	Gly	Gly	
Ser 145	Gly	Gly	Gly	Gly	Ser 150	Gln	Ser	Val	Leu	Thr 155	Gln	Pro	Pro	Ser	Val 160	
Ser 165	Ala	Ala	Pro	Gly	Gln 170	Lys	Val	Thr	Ile	Ser 175	Сүз	Ser	Gly	Ser	Thr	
Ser 180	Asn	Ile	Gly	Asn	Asn 185	Tyr	Val	Ser	Trp	Tyr 190	Gln	Gln	His	Pro	Gly	
Lys 195	Ala	Pro	Lys	Leu	Met 200	Ile	Tyr	Aab	Val	Ser 205	Lys	Arg	Pro	Ser	Gly	
Val 210	Pro	Asp	Arg	Phe	Ser 215	Gly	Ser	Lys	Ser	Gly 220	Asn	Ser	Ala	Ser	Leu	
Asp 225	Ile	Ser	Gly	Leu	Gln 230	Ser	Glu	Asp	Glu	Ala 235	Asp	Tyr	Tyr	Суз	Ala 240	
Ala 245	Trp	Asp	Asp	Ser	Leu 250	Ser	Glu	Phe	Leu	Phe 255	Gly	Thr	Arg	Thr	Lys	
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	Phe	Leu	Phe	Pro	Pro 295	ГЛа	Pro	ГЛа	Asp		Leu	Met	Ile	Ser	Arg	
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	Val	Leu	Thr	Val	Leu 360	His	Gln	Asp	Trp		Asn	Gly	Гла	Glu	Tyr	
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Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr		
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	Val	Lys	Gly	Phe	410 Tyr	Pro	Ser	Asp	Ile		Val	Glu	Trp	Glu	Ser	
		Gln	Pro	Glu	425 Asn	Asn	Tyr	Lys	Thr		Pro	Pro	Val	Leu	Asp	
		Gly	Ser	Phe	440 Phe	Leu	Tyr	Ser	Lys		Thr	Val	Asp	Lys	Ser	
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35 Dh -	<b>F</b> '	a		~7	40	a	F		7	45		P	<b>a</b> 7	<b>a</b> 7	<i>a</i> 7
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Ala 85	Gln	Lys	Leu	Gln	Gly 90	Arg	Val	Thr	Met	Thr 95	Thr	Asb	Thr	Ser	Thr
Ser 100	Thr	Ala	Tyr	Met	Glu 105	Leu	Arg	Ser	Leu	Arg 110	Ser	Asp	Asp	Thr	Ala
Val 115	Tyr	Tyr	Сув	Ala	Arg 120	Val	Pro	Gly	Val	Ser 125	Gly	Ser	Tyr	Pro	Asp
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Ile 165	Gln	Met	Thr	Gln	Ser 170	Pro	Ser	Thr	Leu	Ser 175	Ala	Ser	Ile	Gly	Asp
Arg 180	Val	Thr	Ile	Thr	Cys 185	Arg	Ala	Ser	Glu	Gly 190	Ile	Tyr	His	Trp	Leu
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Pro 405	Gln	Val	Tyr	Thr	Leu 410	Pro	Pro	Ser	Arg	Asp 415	Glu	Leu	Thr	Lys	Asn
Gln 420	Val	Ser	Leu	Thr	Cys 425	Leu	Val	Lys	Gly	Phe 430	Tyr	Pro	Ser	Asp	Ile
Ala 435	Val	Glu	Trp	Glu	Ser 440	Asn	Gly	Gln	Pro	Glu 445	Asn	Asn	Tyr	Lys	Thr

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Als App Tyr Tyr Cys Ala Ala Tup App Tyr Ser Leu Ser Gly Tup Val         245         2460         2470         2480         2480         2490         2490         2490         256         257         258         258         259         250         250         250         250         250         250         250         250         250         250         250         250         250         250         250         250         250         250         251         252         252         253         254         255         255         255         255         255         255         255         255         255         255         255         255         255         255         255	Als Asp Tyr Tyr Cys Ala Ala Trp Asp Tyr Ser Leu Ser Gly Trp Val         245         260       Oly Gly Gly Thr Lys Val Thr Val Leu Cyp Asp Val Arg Glu Pro         275       276         275       277         276       277         276       277         277       277         276       277         277       277         276       277         277       277         278       277         278       277         278       277         278       277         278       277         278       277         278       277         279       277         270       277         270       277         270       277         270       277         270       277         270       277         270       277         270       277         270       277         270       277         270       277         270       277         270       277         270       277 <td< th=""><th></th><th></th><th>-continued</th><th></th></td<>			-continued	
245       250       255         Pine Bill Gily Gily Gily Th: Lye Val Thr Val Leu Gily Amy Val Arg Gilu Pro       225         Lyes Ser Arp Lys Thr Hie Thr Cys Pro Pro Cys Pro Ala Pro Gilu       225         275       286       290         Jong Ser Ser Arp Lys Thr Hie Thr Cys Pro Pro Cys Pro Ala Pro Gilu Ala Pro Gilu 215       280         Leu Leu Gily Gily Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Amp 300       230         290       295       295         Val Ser His Gilu Amp Pro Gilu Val Lys Phe Am Trp Tyr Val Amp Gily 320       320         216       700       200         216       110 Yal Yar Yu Yal Yal Ser Val Lys Pro Arg Gilu Gilu Gilu Gil Tyr Am 350         300       300       300         216       111 Yr Arg Val Val Ser Val Lyu Trr Lys Pro Arg Gilu Gilu Gilu Am Arg Tirp 355         210       111 Yr Tri Leu Pro Pro Ser Arg Amp Gily Gily Oli Pro Arg Gilu 356         210       211 Yr Tir Leu Pro Pro Ser Arg Amp Gilu Leu Thr Lye Am 415         210       211 Yr Thr Leu Pro Pro Ser Arg Amp Gilu Leu Thr Lye For 400         210       212       224         210       212       214 Gilu Am An Tyr Lye Tyr Ero Ser Amp Tip 440         210       210       210       210         210       210       210       210         210       210 </td <td>245       250       255         Phe Gly Gly Gly Gly Gly Thi Lys Val Thr Val Leu Gly Asp Val Arg Glu Pro       265         Lys Ser Ser Aep Lys Thr Hin Thr Cys Pro Pro Cyu Pro Ala Pro Glu       200         275       200       201 Gly Gly Gly Gly Pro Jer Val Phe Leu Pro Pro Cyu Pro Jaka Pro Glu Val Pro Jaca Pro Java Pro Java Pro Java Pro Java Pro Java Pro Glu Val Pro Java Pro Cyu Val Val Val Val Val Asp Java Pro Glu Val Pro Glu Val Pro Arg Glu Glu Glu Glu Glu Pro Pro Java Pro Glu Val Pro Pro Arg Glu Glu Glu Glu Try Pro Java Pro Pro Val Pro Java Pro Pro Pro Val Pro Java Pro Pro Pro Val Pro Pro Pro Pro Pro Pro Pro Pro Val Pro Java Pro Glu Pro Pro Val Pro Java Pro Pro Pro Val Pro Pro Val Pro Pro Pro Val Pro Pro Pro Val Pro Pro Pro Val Pro Ha Pro Pro Val Pro Pro Pro Val Pro Pro Pro Val Pro Pro Pro Val Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro</td> <td>225</td> <td>230 235</td> <td>240</td> <td></td>	245       250       255         Phe Gly Gly Gly Gly Gly Thi Lys Val Thr Val Leu Gly Asp Val Arg Glu Pro       265         Lys Ser Ser Aep Lys Thr Hin Thr Cys Pro Pro Cyu Pro Ala Pro Glu       200         275       200       201 Gly Gly Gly Gly Pro Jer Val Phe Leu Pro Pro Cyu Pro Jaka Pro Glu Val Pro Jaca Pro Java Pro Java Pro Java Pro Java Pro Java Pro Glu Val Pro Java Pro Cyu Val Val Val Val Val Asp Java Pro Glu Val Pro Glu Val Pro Arg Glu Glu Glu Glu Glu Pro Pro Java Pro Glu Val Pro Pro Arg Glu Glu Glu Glu Try Pro Java Pro Pro Val Pro Java Pro Pro Pro Val Pro Java Pro Pro Pro Val Pro Pro Pro Pro Pro Pro Pro Pro Val Pro Java Pro Glu Pro Pro Val Pro Java Pro Pro Pro Val Pro Pro Val Pro Pro Pro Val Pro Pro Pro Val Pro Pro Pro Val Pro Ha Pro Pro Val Pro Pro Pro Val Pro Pro Pro Val Pro Pro Pro Val Pro	225	230 235	240	
240       226       270         Lys Ser Ser Ap Lys Thi His Thr Cys Pro Pro Cys Pro Ala Pro Glu       280         275       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       281         280       281       281         281       281       280         282       281       281         283       281       281         284       281       281         285       281       281         281       281       281         282       281       291         283       291       291         284       291       291         285       291       291 <td< td=""><td>240       226       270         Lys Ser Ser Ap Lys Thi His Thr Cys Pro Pro Cys Pro Ala Pro Glu       280         275       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       281         280       281       281         281       281       280         282       281       281         283       281       281         284       281       281         285       281       281         281       281       281         282       281       291         283       291       291         284       291       291         285       291       291         <td< td=""><td></td><td></td><td>Leu Ser Gly Trp Val</td><td></td></td<></td></td<>	240       226       270         Lys Ser Ser Ap Lys Thi His Thr Cys Pro Pro Cys Pro Ala Pro Glu       280         275       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       280         280       280       281         280       281       281         281       281       280         282       281       281         283       281       281         284       281       281         285       281       281         281       281       281         282       281       291         283       291       291         284       291       291         285       291       291 <td< td=""><td></td><td></td><td>Leu Ser Gly Trp Val</td><td></td></td<>			Leu Ser Gly Trp Val	
275       280       285         Leu Leu Cly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp 300       300         775       Leu Leu Cly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Val Val Val Val Asp 310       315         3005       310       315       300         775       Leu Met Cle Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Pap Gly 335       316         310       317       326       317         321       320       326       327         321       320       328       320         321       320       325       320         321       320       325       320         321       320       325       320         323       320       325       320         323       320       325       320         325       Statt Statt       Statt Statt       Statt Statt         326       Statt Statt       Statt Statt       Statt Statt       Statt Statt         326       Statt Statt Statt	275       280       285         Leu Leu Cly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp 300       300         775       Leu Leu Cly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Val Val Val Val Asp 310       315         3005       310       315       300         775       Leu Met Cle Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Pap Gly 335       316         310       317       326       317         321       320       326       327         321       320       328       320         321       320       325       320         321       320       325       320         321       320       325       320         323       320       325       320         323       320       325       320         325       Statt Statt       Statt Statt       Statt Statt         326       Statt Statt       Statt Statt       Statt Statt       Statt Statt         326       Statt Statt Statt			Asp Val Arg Glu Pro	
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Ser Thr Tyr Arg Val Val Ser Val Leu Thr Yal Leu His Gln Asp Trp 365         Leu Ann Gly Lys Glu Tyr Lys Cys Lys Val Ser Ann Lys Ala Leu Pro 375         Jan Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu 395         Jas Pro Ile Glu Lys Thr Leu Pro Pos Arg Apg Glu Leu Thr Lys Ann 400         Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile 425         Ha Glu Trg Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr 435         Ha Glu Trg Glu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys 460         Heu Ner Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys 480         Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu 495         Val Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu 495         Val Den Ser Val Leu Ser Pro Gly Lys         Ser Cale Ser Pro Gly Lys         Val Den Ser Val Leu Ser Pro Gly Lys         Val Den Ser Line Sequence         Valor Seguerce: Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu 495         Valor Seguerce: Nor         Valor Seguerce: Valor         Valor Seguerce: Va	Ser Thr Tyr Arg Val Val Ser Val Leu Thr Yal Leu His Gln Asp Trp 365         Leu Ann Gly Lys Glu Tyr Lys Cys Lys Val Ser Ann Lys Ala Leu Pro 375         Jan Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu 395         Jas Pro Ile Glu Lys Thr Leu Pro Pos Arg Apg Glu Leu Thr Lys Ann 400         Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile 425         Ha Glu Trg Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr 435         Ha Glu Trg Glu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys 460         Heu Ner Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys 480         Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu 495         Val Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu 495         Val Den Ser Val Leu Ser Pro Gly Lys         Ser Cale Ser Pro Gly Lys         Val Den Ser Val Leu Ser Pro Gly Lys         Val Den Ser Line Sequence         Valor Seguerce: Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu 495         Valor Seguerce: Nor         Valor Seguerce: Valor         Valor Seguerce: Va			Glu Glu Gln Tyr Asn	
Leu Aan Giy Lye Giu Tyr Lye Cys Lye Yal Ser Aan Lye Ala Leu Pro 370 375 375 375 380 380 380 380 380 380 380 380 380 380	Leu Aan Giy Lye Giu Tyr Lye Cys Lye Yal Ser Aan Lye Ala Leu Pro 370 375 375 375 380 380 380 380 380 380 380 380 380 380	Ser Thr Tyr Arg Val	Val Ser Val Leu Thr Val 3	Leu His Gln Asp Trp	
Ala Pro Ile Glu LysThr Ile Ser LysAla LysGly Gln Pro ArgGlu 400385NoTyr Thr 410Leu Pro Pro Ser Arg 415App Glu Leu Thr 415LysAsn 415Gln Val Ser Leu Thr 420CysLeu Thr 425LysGly Phe 415Tyr Pro Ser Arg 415AsnAla Val Glu Trp Glu Ser Aen Gly Gln Pro 455Glu Asn Asn Tyr LysThr 445Thr 446Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe 455Phe Leu Tyr Ser Lys 455Thr 480Ser Val Met His Glu Ala Leu His Asn His 490Tyr Thr Gln Lys Ser Leu 495Ser Leu 495Ser Leu Ser Pro Gly LysSer 211>Expuence 421>Sequence 421>4210AspSer AspGly Cence 495Sequence4210AspSer AspGly Cence 495Ser Leu 495485AspGly Cence 495Ser Leu 495486AspGly Cence 495Ser Leu 495 <td>Ala Pro Ile Glu LysThr Ile Ser LysAla LysGly Gln Pro ArgGlu 400385NoTyr Thr 410Leu Pro Pro Ser Arg 415App Glu Leu Thr 415LysAsn 415Gln Val Ser Leu Thr 420CysLeu Thr 425LysGly Phe 415Tyr Pro Ser Arg 415AsnAla Val Glu Trp Glu Ser Aen Gly Gln Pro 455Glu Asn Asn Tyr LysThr 445Thr 446Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe 455Phe Leu Tyr Ser Lys 455Thr 480Ser Val Met His Glu Ala Leu His Asn His 490Tyr Thr Gln Lys Ser Leu 495Ser Leu 495Ser Leu Ser Pro Gly LysSer 211&gt;Expuence 421&gt;Sequence 421&gt;4210AspSer AspGly Cence 495Sequence4210AspSer AspGly Cence 495Ser Leu 495485AspGly Cence 495Ser Leu 495486AspGly Cence 495Ser Leu 495<td>Leu Asn Gly Lys Glu</td><td>Tyr Lys Cys Lys Val Ser .</td><td>Asn Lys Ala Leu Pro</td><td></td></td>	Ala Pro Ile Glu LysThr Ile Ser LysAla LysGly Gln Pro ArgGlu 400385NoTyr Thr 410Leu Pro Pro Ser Arg 415App Glu Leu Thr 415LysAsn 415Gln Val Ser Leu Thr 420CysLeu Thr 425LysGly Phe 415Tyr Pro Ser Arg 415AsnAla Val Glu Trp Glu Ser Aen Gly Gln Pro 455Glu Asn Asn Tyr LysThr 445Thr 446Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe 455Phe Leu Tyr Ser Lys 455Thr 480Ser Val Met His Glu Ala Leu His Asn His 490Tyr Thr Gln Lys Ser Leu 495Ser Leu 495Ser Leu Ser Pro Gly LysSer 211>Expuence 421>Sequence 421>4210AspSer AspGly Cence 495Sequence4210AspSer AspGly Cence 495Ser Leu 495485AspGly Cence 495Ser Leu 495486AspGly Cence 495Ser Leu 495 <td>Leu Asn Gly Lys Glu</td> <td>Tyr Lys Cys Lys Val Ser .</td> <td>Asn Lys Ala Leu Pro</td> <td></td>	Leu Asn Gly Lys Glu	Tyr Lys Cys Lys Val Ser .	Asn Lys Ala Leu Pro	
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Gin Val Ser Leu Thr Cyg Leu Val Lyg Gip Phe Tyr Pro Ser Asp Ile 420 Ala Val Giu Tr Giu Ser Asn Gip Gin Pro Giu Asn Asn Tyr Lyg Thr 435 Ala Val Giu Tr Giu Ser Asn Gip Gir Phe Phe Leu Tyr Ser Lyg 450 450 455 450 Leu Thr Val Asp Lyg Ser Arg Trp Gin Gin Gip Asn Val Phe Ser Cyg 470 470 470 470 470 475 470 475 470 475 470 475 470 475 470 475 470 475 475 470 475 475 475 475 475 475 475 475	Gin Val Ser Leu Thr Cyg Leu Val Lyg Gip Phe Tyr Pro Ser Asp Ile 420 Ala Val Giu Tr Giu Ser Asn Gip Gin Pro Giu Asn Asn Tyr Lyg Thr 435 Ala Val Giu Tr Giu Ser Asn Gip Gir Phe Phe Leu Tyr Ser Lyg 450 450 455 450 Leu Thr Val Asp Lyg Ser Arg Trp Gin Gin Gip Asn Val Phe Ser Cyg 470 470 470 470 470 475 470 475 470 475 470 475 470 475 470 475 470 475 475 470 475 475 475 475 475 475 475 475	Pro Gln Val Tyr Thr	Leu Pro Pro Ser Arg Asp		
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr 445 Thr Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys 450 Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys 470 475 470 477 470 477 477 480 Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu 495 495 495 495 495 495 495 495	Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr 445 Thr Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys 450 Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys 470 475 470 477 470 477 477 480 Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu 495 495 495 495 495 495 495 495	Gln Val Ser Leu Thr	Cys Leu Val Lys Gly Phe	Tyr Pro Ser Asp Ile	
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys 450 Pro Val Leu Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys 465 470 470 475 480 Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu 490 490 490 495 Ser Leu Ser Pro Gly Lys 500 <210> SEQ ID NO 200 <211> LENGTH: 1497 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FFATURE: <214> NMR/KEY: source <221> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolynucleotide" <400> SEQUENCE: 200 atggaagcac cagcgcagct totottocto dgctactot ggctoccaga taccaccggt 60 gaggtgcagc tggtggagac tggggaaggc ctggtcaagc ctggtggagt ccgcaggct 120 tcctgtacag cototggatt caccttcagg agttatagct tgaactggt ccgcaggct 180 ccagggcagg ggctggagtg ggtotcatcc attagtagta ctagtactta catatactac 240 gaggactcgg tgaagggcc gattcaccat tccagagacg acgccaagaa caccatgtat 300	Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys 450 Pro Val Leu Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys 465 470 470 475 480 Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu 490 490 490 495 Ser Leu Ser Pro Gly Lys 500 <210> SEQ ID NO 200 <211> LENGTH: 1497 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FFATURE: <214> NMR/KEY: source <221> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolynucleotide" <400> SEQUENCE: 200 atggaagcac cagcgcagct totottocto dgctactot ggctoccaga taccaccggt 60 gaggtgcagc tggtggagac tggggaaggc ctggtcaagc ctggtggagt ccgcaggct 120 tcctgtacag cototggatt caccttcagg agttatagct tgaactggt ccgcaggct 180 ccagggcagg ggctggagtg ggtotcatcc attagtagta ctagtactta catatactac 240 gaggactcgg tgaagggcc gattcaccat tccagagacg acgccaagaa caccatgtat 300	Ala Val Glu Trp Glu	Ser Asn Gly Gln Pro Glu .	Asn Asn Tyr Lys Thr	
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35 40 45	
Phe Arg Ser Tyr Ser Leu Asn Trp Val Arg Gln Ala Pro Gly Gln Gly 50 55 60	
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Lys 465	Ser	Arg	Trp	Gln	Gln 470	Gly	Asn	Val	Phe	Ser 475	Суз	Ser	Val	Met	His 480
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435 440 445 Tyr Lys Thr Thr Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu 450 455 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val 455 440 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln 485 500 505 210> SEQ ID NO 208 <211> LENGTH: 1503 <212> TYPE DNA 212> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <222> OTHER INFORMATION: /note="Description of Artificial Sequence: syntheticpolynucleotide" <400> SEQUENCE: 208 atggaagcaac cagegcagct totottocot ctgctactot ggctcocaga taccaccgst for gaagtgcagc tggtgcagtc tggggctgaa gtgaagaagac ctggggccta atggaaggtc tottgtcagg cttctggata caccttcagc ggcactata tgcacttggt gcgacaggcc 180 ccggacacag ggcttgatg gatgggggtgg atccacccta ccggtggtg cacaacctat 240	420 425 430	
450 455 460 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val 465 470 475 480 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln 485 490 495 Lys Ser Leu Ser Leu Ser Pro Gly Lys 500 505 <210> SEQ ID NO 208 <211> LENGTH: 1503 <212> TYPE: DNA 213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolynucleotide" <400> SEQUENCE: 208 atggaagcaac cagegeaget tetetteete tggeteecaga taceaceggt 60 gaagtgeage tggtgeagte tggggetgaa gtgaagaage etggggeete agtgaaggte 120 tettgteagg ettetggata cacetteage gggeaetata tgeaettggt gegacaggee 180 ectggacaag ggettgagtg gatgggggtg atceacecta ccagtggtgg cacaacetat 240		
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atggaagcac cagegeaget tetetteete etgetaetet ggeteeeaga taeeaeeggt 60 gaagtgeage tggtgeagte tggggetgaa gtgaagaage etgggggeete agtgaaggte 120 tettgteagg ettetggata eacetteage gggeaetata tgeaettggt gegaeaggee 180 eetggaeaag ggettgagtg gatggggtgg ateeaeeeta eeagtggtgg eacaaeetat 240	<211> LENGTH: 1503 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence	
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115									-	-	-			_	-
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Gln 165	Pro	Ser	Ser	Val	Ser 170	Gly	Ala	Pro	Gly	Gln 175	Arg	Val	Thr	Ile	Ser
Cys 180	Thr	Gly	Ser	Ser	Ser 185	Asn	Ile	Gly	Ala	Gly 190	Tyr	Asp	Val	Asn	Trp
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Val 340	. His	Asn	Ala	Lys	Thr 345	Lys	Pro	Arg	Glu	Glu 350	Gln	Tyr	Asn	Ser	Thr
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Phe T 50	hr	Asn	His	Trp	Ile 55	Ala	Trp	Val	Arg	Gln 60	Met	Pro	Gly	Lys	Gly
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Leu T 370					375					380					
Lуя V 385					390					395					400
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Met       Glu       Ala       Pro       Ala       Glu       Leu       Pro       Leu       Tru       Leu       Pro       Leu       Pro         Asp       Thr       Glu       Glu       Met       Glu       Leu       Pro       Leu       Tru       Leu       Pro         Asp       Thr       Glu       Glu       Met       Met       Su       Leu       Pro       Su       Val         Asp       Thr       Glu       Glu       Met       Met       Met       Val       Su       Val       Val         Glu       Pro       Glu       Arg       Leu       Su       Su       Glu       Val       Val         Glu       Pro       Glu       Arg       Leu       Su       Su       Glu       Val       Val         Su       Glu       Arg       Leu       Su       Su       Ala       Su       Glu       Pro       Hu       Tru         Su       Su       Tru       Val       Arg       Cu       Su       Arg       Su       Su       Su       Tru       Su       Su       Su       Su       Su       Su       Su       Su       Su	<211> LENGTH: 502 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificia	l Sequence:
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20       25       30         Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr         35       40       45         Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly         50       55         Leu Glu Trp Val Ala Val Ile Ser Tyr Asp Gly Ser Ile Lys Tyr Tyr		
35     40     45       Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly     50       50     55     60       Leu Glu Trp Val Ala Val Ile Ser Tyr Asp Gly Ser Ile Lys Tyr Tyr		Val Val
50     55     60       Leu Glu Trp Val Ala Val Ile Ser Tyr Asp Gly Ser Ile Lys Tyr Tyr		Phe Thr
		Lys Gly
Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys 85 90 95		Ser Lys

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Asn 100	Thr	Leu	Tyr	Leu	Gln 105	Met	Asn	Ser	Leu	Arg 110	Ala	Glu	Asp	Thr	Gly					
Val 115	Tyr	Tyr	Сув	Ser	Lys 120	Asp	Arg	Tyr	Ser	Ser 125	Gly	Trp	Tyr	Ser	Ser					
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Arg 180	Ile	Thr	Cys	Gln	Gly 185	Asp	Ser	Leu	Arg	Ser 190	Tyr	Tyr	Ala	Ser	Trp					
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Lys 275	Ser	Ser	Asp	Lys	Thr 280	His	Thr	Суз	Pro	Pro 285	Суз	Pro	Ala	Pro	Glu					
Leu 290	Leu	Gly	Gly	Pro	Ser 295	Val	Phe	Leu	Phe	Pro 300	Pro	Lys	Pro	Lys	Asp					
Thr 305	Leu	Met	Ile	Ser	Arg 310	Thr	Pro	Glu	Val	Thr 315	Суз	Val	Val	Val	Aap 320					
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Val 340	Glu	Val	His	Asn	Ala 345	Lys	Thr	Lys	Pro	Arg 350	Glu	Glu	Gln	Tyr	Asn					
Ser 355	Thr	Tyr	Arg	Val	Val 360	Ser	Val	Leu	Thr	Val 365	Leu	His	Gln	Asp	Trp					
Leu 370	Asn	Gly	Lys	Glu	Tyr 375	Lys	Сүз	Lys	Val	Ser 380	Asn	ГÀа	Ala	Leu	Pro					
Ala 385	Pro	Ile	Glu	ГÀа	Thr 390	Ile	Ser	ГÀа	Ala	Lys 395	Gly	Gln	Pro	Arg	Glu 400					
Pro 405	Gln	Val	Tyr	Thr	Leu 410	Pro	Pro	Ser	Arg	Asp 415	Glu	Leu	Thr	Lys	Asn					
Gln 420	Val	Ser	Leu	Thr	Cys 425	Leu	Val	Lys	Gly	Phe 430	Tyr	Pro	Ser	Asp	Ile					
Ala 435	Val	Glu	Trp	Glu	Ser 440	Asn	Gly	Gln	Pro	Glu 445	Asn	Asn	Tyr	Lys	Thr					
Thr 450	Pro	Pro	Val	Leu	Asp 455	Ser	Asp	Gly	Ser	Phe 460	Phe	Leu	Tyr	Ser	Lys					
Leu 465	Thr	Val	Asp	Lys	Ser 470	Arg	Trp	Gln	Gln	Gly 475	Asn	Val	Phe	Ser	Суз 480					
Ser 485	Val	Met	His	Glu	Ala 490	Leu	His	Asn	His	Tyr 495	Thr	Gln	Lys	Ser	Leu					
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Gln 35	Pro	Gly	Arg	Ser	Leu 40	Arg	Leu	Ser	Cys	Ala 45	Ala	Ser	Gly	Phe	Thr
Phe 50	Ser	Ser	Tyr	Gly	Met 55	His	Trp	Val	Arg	Gln 60	Ala	Pro	Gly	Lys	Gly
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Thr 180	Ile	Ser	Суз	Ser	Gly 185	Ser	Ser	Ser	Asn	Ile 190	Gly	Ser	Asn	Thr	Val
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Arg 260	Val	Phe	Gly	Gly	Gly 265	Thr	Lys	Leu	Thr	Val 270	Leu	Gly	Asp	Val	Arg
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Val 325	Asp	Val	Ser	His	Glu 330	Asp	Pro	Glu	Val	Lys 335	Phe	Asn	Trp	Tyr	Val
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Tyr 355	Asn	Ser	Thr	Tyr	Arg 360	Val	Val	Ser	Val	Leu 365	Thr	Val	Leu	His	Gln
Asp 370	Trp	Leu	Asn	Gly	Lys 375	Glu	Tyr	Lys	Суз	Lуя 380	Val	Ser	Asn	Lys	Ala
Leu 385	Pro	Ala	Pro	Ile	Glu 390	ГЛЗ	Thr	Ile	Ser	Lys 395	Ala	ГЛа	Gly	Gln	Pro 400

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Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr 405 410 415 Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser 420 425 430 Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr 435 440 445 Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr 450 455 460 Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe 465 475 470 480 Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys 485 490 495 Ser Leu Ser Leu Ser Pro Gly Lys 500 <210> SEQ ID NO 220 <211> LENGTH: 1488 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolynucleotide" <400> SEQUENCE: 220 atggaagcac cagegeaget tetetteete etgetaetet ggeteecaga taccaeeggt 60 caggtgcage tggtgcagte tgggggagge ttggtccage egggggggte cetgagaete 120 teetgtgeag cetetggatt caegtttagt acetatgeea tgagttggge eegeeagget 180  $\verb|ccagggaagg ggctggagtg ggtctcaagt attagtggtg atggtggaag aattctcgat|$ 240 gcagacteeg egaagggeeg gtteaceate teeagagaea atteeaagaa eaegetgtat 300 ctgcaaatga acggcctgag agtcgaggac acggcccttt attactgtgc gagagcggac 360 ggtaactact ggggcagggg gacaatggtc accgtctctt caggtggagg cggttcaggc 420 ggaggtggca gcggcggtgg cggatcgcag tctgtgctga ctcagcctgc ctccgtgtct 480 gggtctcctg gacagtcgat caccatctcc tgcactggaa ccagcagtga cgttggtggt 540 tataactatg tctcctggta ccaacaacac ccaggcaaag cccccaaact catgatttat 600 gagggcagta agcggccctc aggggtttct aatcgcttct ctggctccaa gtctggcaac 660 acggeeteee tgacaatete tgggeteeag getgaggaeg aggetgatta ttaetgeage 720 tcatatacaa ccaggagcac tcgagttttc ggcggaggga ccaagctgac cgtcctaggt 780 gacgtacgcg agcccaaatc ttctgacaaa actcacacat gcccaccgtg cccagcacct 840 gaacteetgg gtggacegte agtetteete tteeeceaa aaeeeaagga caeeeteatg 900 960 atctcccgga cccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 1020 gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1080 tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc 1140 gagaaaacca tetecaaage caaagggeag eeeegagaae cacaggtgta caceetgeee 1200 ccatcccqqq atqaqctqac caaqaaccaq qtcaqcctqa cctqcctqqt caaaqqcttc 1260

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Thr 275	Суз	Pro	Pro	Суз	Pro 280	Ala	Pro	Glu	Leu	Leu 285	Gly	Gly	Pro	Ser	Val		
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Ser 385	Lys	Ala	Lys	Gly	Gln 390	Pro	Arg	Glu	Pro	Gln 395	Val	Tyr	Thr	Leu	Pro 400	
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-			-						-				-		agactc	
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Asn 210	Arg	Pro	Ser	Gly	Ile 215	Pro	Asp	Arg	Phe	Ser 220	Gly	Ser	Ser	Ser	Gly				
Asn 225	Thr	Ala	Ser	Leu	Thr 230	Ile	Thr	Gly	Ala	Gln 235	Ala	Glu	Asp	Glu	Ala 240				
Asp 245	Tyr	Tyr	Сүз	Asn	Ser 250	Arg	Asp	Ser	Ser	Gly 255	Asn	His	Val	Val	Phe				
Gly 260	Gly	Gly	Thr	Lys	Leu 265	Thr	Val	Leu	Gly	Asp 270	Val	Arg	Glu	Pro	Гла				
Ser 275	Ser	Asp	Lys	Thr	His 280	Thr	Cys	Pro	Pro	Сув 285	Pro	Ala	Pro	Glu	Leu				
Leu 290	Gly	Gly	Pro	Ser	Val 295	Phe	Leu	Phe	Pro	Pro 300	Гла	Pro	Lys	Asp	Thr				
Leu 305	Met	Ile	Ser	Arg	Thr 310	Pro	Glu	Val	Thr	Cys 315	Val	Val	Val	Asp	Val 320				
Ser 325	His	Glu	Asp	Pro	Glu 330	Val	Lys	Phe	Asn	Trp 335	Tyr	Val	Asp	Gly	Val				
Glu 340	Val	His	Asn	Ala	Lys 345	Thr	Lys	Pro	Arg	Glu 350	Glu	Gln	Tyr	Asn	Ser				
Thr 355	Tyr	Arg	Val	Val	Ser 360	Val	Leu	Thr	Val	Leu 365	His	Gln	Asp	Trp	Leu				
Asn 370	Gly	Lys	Glu	Tyr	Lys 375	Суз	Lys	Val	Ser	Asn 380	ГЛа	Ala	Leu	Pro	Ala				
Pro 385	Ile	Glu	ГЛа	Thr	Ile 390	Ser	Lys	Ala	Lys	Gly 395	Gln	Pro	Arg	Glu	Pro 400				
Gln 405	Val	Tyr	Thr	Leu	Pro 410	Pro	Ser	Arg	Asp	Glu 415	Leu	Thr	Lys	Asn	Gln				
Val 420	Ser	Leu	Thr	Суз	Leu 425	Val	Lys	Gly	Phe	Tyr 430	Pro	Ser	Asp	Ile	Ala				
Val 435	Glu	Trp	Glu	Ser	Asn 440	Gly	Gln	Pro	Glu	Asn 445	Asn	Tyr	Lys	Thr	Thr				
Pro 450	Pro	Val	Leu	Asp	Ser 455	Asp	Gly	Ser	Phe	Phe 460	Leu	Tyr	Ser	Lys	Leu				
Thr 465	Val	Asp	Lys	Ser	Arg 470	Trp	Gln	Gln	Gly	Asn 475	Val	Phe	Ser	Суз	Ser 480				
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		EQUEN																	
atgg															cccggt	60 120			
a 2 a a a	rugua	aye t	Jycag	Jyayı	u ge	99090	Layya	a cuç	JArda	aaye	000	-9999	jac (	lorgt	COOLO	120			
cagg	acar	nta t	- at a	aatr	na ci	tacet	taad		aat	act	aat	ndadi	ta /	ato	gccag	180			

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gacagcetca gaagetatta tgeaagetgg taecageaga ageeaggaea ggeeeetgta	600
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Pro 130	Asp	Tyr	Trp	Gly	Gln 135	Gly	Thr	Leu	Val	Thr 140	Val	Ser	Ser	Gly	Gly
Gly 145	Gly	Ser	Gly	Gly	Gly 150	Gly	Ser	Gly	Gly	Gly 155	Gly	Ser	Ser	Glu	Leu 160
Thr 165	Gln	Asp	Pro	Ala	Val 170	Ser	Val	Ala	Leu	Gly 175	Gln	Thr	Val	Arg	Ile
Thr 180	Суз	Gln	Gly	Asp	Ser 185	Leu	Arg	Ser	Tyr	Tyr 190	Ala	Ser	Trp	Tyr	Gln
Gln 195	Lys	Pro	Gly	Gln	Ala 200	Pro	Val	Leu	Val	Ile 205	Tyr	Gly	Lys	Asn	Asn
Arg 210	Pro	Ser	Gly	Ile	Pro 215	Asp	Arg	Phe	Ser	Gly 220	Ser	Ser	Ser	Gly	Asn
Thr 225	Ala	Ser	Leu	Thr	Ile 230	Thr	Gly	Ala	Gln	Ala 235	Glu	Asp	Glu	Ala	Asp 240
Tyr 245	Tyr	Суз	Asn	Ser	Arg 250	Asp	Ser	Ser	Gly	Asn 255	His	Val	Val	Phe	Gly
Gly 260	Gly	Thr	Lys	Leu	Thr 265	Val	Leu	Gly	Asp	Val 270	Arg	Glu	Pro	Lys	Ser
	Asp	Lys	Thr	His		Суз	Pro	Pro	Суз		Ala	Pro	Glu	Leu	Leu
	Gly	Pro	Ser	Val		Leu	Phe	Pro	Pro		Pro	Lys	Asp	Thr	Leu
	Ile	Ser	Arg	Thr		Glu	Val	Thr	Суз		Val	Val	Asp	Val	Ser 320
	Glu	Asp	Pro	Glu		Lys	Phe	Asn	Trp		Val	Asp	Gly	Val	
	His	Asn	Ala	Lys		Lys	Pro	Arg	Glu		Gln	Tyr	Asn	Ser	Thr
	Arg	Val	Val	Ser		Leu	Thr	Val	Leu		Gln	Asp	Trp	Leu	Asn
Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro
	Glu	Lys	Thr	Ile		Lys	Ala	Lys	Gly		Pro	Arg	Glu	Pro	
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405 Ser	Leu	Thr	Суз	Leu	410 Val		Gly	Phe	Tyr	415 Pro	Ser	Asp	Ile	Ala	Val
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435					440					445	-	-			
450			-		455	•				460	•		-		
465		-		5	470			-		475			-		480
485				Leu	His 490	Asn	His	Tyr	Thr	Gln 495	ГЛЗ	Ser	Leu	Ser	Leu
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	Pro	Gly	Gly	Ser		Arg	Leu	Ser	Cys		Ala	Ser	Gly	Phe	Thr
	Ser	Ser	Tyr	Gly		His	Trp	Val	Arg		Ala	Pro	Gly	Lys	Gly
	Glu	Trp	Val	Ala		Ile	Phe	Tyr	Asp		Gly	Asn	Lys	Tyr	Tyr 80
	Asp	Ser	Val	Lys		Arg	Phe	Thr	Ile		Arg	Asp	Asn	Ser	
	Thr	Leu	Tyr	Leu		Met	Asn	Ser	Leu		Ala	Glu	Asp	Thr	Ala
Val 115	Tyr	Tyr	Суз	Ala	Arg 120	Asp	Arg	Gly	Tyr	Tyr 125	Tyr	Met	Asp	Val	Trp
Gly 130	Lys	Gly	Thr	Thr	Val 135	Thr	Val	Ser	Ser	Gly 140	Gly	Gly	Gly	Ser	Gly
Gly 145	Gly	Gly	Ser	Gly	Gly 150	Gly	Gly	Ser	Gln	Ser 155	Val	Leu	Thr	Gln	Pro 160
Pro 165	Ser	Val	Ser	Gly	Ala 170	Pro	Gly	Gln	Arg	Val 175	Thr	Ile	Ser	Cys	Thr
Gly 180	Arg	Ser	Ser	Asn	Ile 185	Gly	Ala	Gly	His	Asp 190	Val	His	Trp	Tyr	Gln
Gln 195	Leu	Pro	Gly	Thr	Ala 200	Pro	Lys	Leu	Leu	Ile 205	Tyr	Gly	Asp	Ser	Asn
Arg 210	Pro	Ser	Gly	Val	Pro 215	Asp	Arg	Phe	Ser	Gly 220	Ser	Arg	Ser	Gly	Thr
Ser 225	Ala	Ser	Leu	Ala	Ile 230	Thr	Gly	Leu	Gln	Ala 235	Glu	Asp	Glu	Ala	Asp 240
Tyr 245	Tyr	Cys	Gln	Ser	Tyr 250	Asp	Ser	Ser	Leu	Arg 255	Gly	Ser	Val	Phe	Gly
Gly 260	Gly	Thr	Lys	Val	Thr 265	Val	Leu	Gly	Asp	Val 270	Arg	Glu	Pro	Lys	Ser
Ser 275	Asp	Lys	Thr	His	Thr 280	Сүз	Pro	Pro	Суз	Pro 285	Ala	Pro	Glu	Leu	Leu
Gly 290	Gly	Pro	Ser	Val	Phe 295	Leu	Phe	Pro	Pro	Lys 300	Pro	Lys	Asp	Thr	Leu
Met 305	Ile	Ser	Arg	Thr	Pro 310	Glu	Val	Thr	Сув	Val 315	Val	Val	Asp	Val	Ser 320
His 325	Glu	Asp	Pro	Glu	Val 330	Гла	Phe	Asn	Trp	Tyr 335	Val	Asp	Gly	Val	Glu
Val 340	His	Asn	Ala	Гла	Thr 345	Гла	Pro	Arg	Glu	Glu 350	Gln	Tyr	Asn	Ser	Thr
Tyr 355	Arg	Val	Val	Ser	Val 360	Leu	Thr	Val	Leu	His 365	Gln	Asp	Trp	Leu	Asn
Gly 370	Lys	Glu	Tyr	Lys	Сув 375	Lys	Val	Ser	Asn	Lys 380	Ala	Leu	Pro	Ala	Pro
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Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr	
450 455 460	
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val 465 470 475 480	
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Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro 435 440 445
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val 450 455 460
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Ser 145	Gly	Gly	Gly	Gly	Ser 150	Gly	Gly	Gly	Gly	Ser 155	Ala	Gln	Ser	Val	Leu 160
Thr 165	Gln	Pro	Pro	Ser	Val 170	Ser	Val	Ala	Pro	Gly 175	Gln	Thr	Ala	Arg	Ile
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	Asp	Lys	Ser	Arg	455 Trp	Gln	Gln	Gly	Asn		Phe	Ser	Суз	Ser	
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nec 1	<i>a</i> 1				T en	Cruc	7.000	<b>W</b> 2620	c)	Lev	Lev	T en	710	Lou	Lou
T	Glu				Leu	СЛа	Arg	Trp	Gly 10	Leu	Leu	Leu	Ala	Leu 15	Leu
		Leu	Ala	Ala 5	Leu Ser 25	-	_	_	10					15	
Pro 20	Pro	Leu Gly	Ala Ala	Ala 5 Ala	Ser	Thr	Gln	Val	10 Суз	Thr 30	Gly	Thr	Asp	15 Met	Lys
Pro 20 Leu 35	Pro Arg	Leu Gly Leu	Ala Ala Pro	Ala 5 Ala Ala	Ser 25 Ser	Thr Pro	Gln Glu	Val Thr	10 Cys His	Thr 30 Leu 45	Gly	Thr Met	Asp Leu	15 Met Arg	Lys His
Pro 20 Leu 35 Leu 50	Pro Arg Tyr	Leu Gly Leu Gln	Ala Ala Pro Gly	Ala 5 Ala Ala Cys	Ser 25 Ser 40 Gln	Thr Pro Val	Gln Glu Val	Val Thr Gln	10 Cys His Gly	Thr 30 Leu 45 Asn 60	Gly Asp Leu	Thr Met Glu	Asp Leu Leu	15 Met Arg Thr	Lys His Tyr
Pro 20 Leu 35 Leu 50 Leu 65	Pro Arg Tyr Pro	Leu Gly Leu Gln Thr	Ala Ala Pro Gly Asn	Ala 5 Ala Ala Cys Ala	Ser 25 Ser 40 Gln 55 Ser	Thr Pro Val Leu	Gln Glu Val Ser	Val Thr Gln Phe	10 Cys His Gly Leu	Thr 30 Leu 45 Asn 60 Gln 75	Gly Asp Leu Asp	Thr Met Glu Ile	Asp Leu Leu Gln	15 Met Arg Thr Glu	Lys His Tyr Val 80
Pro 20 Leu 35 Leu 50 Leu 65 Gln 85	Pro Arg Tyr Pro Gly	Leu Gly Leu Gln Thr Tyr	Ala Ala Pro Gly Asn Val	Ala 5 Ala Ala Cys Ala Leu	Ser 25 Ser 40 Gln 55 Ser 70 Ile	Thr Pro Val Leu Ala	Gln Glu Val Ser His	Val Thr Gln Phe Asn	10 Cys His Gly Leu Gln	Thr 30 Leu 45 Asn 60 Gln 75 Val 95	Gly Asp Leu Asp Arg	Thr Met Glu Ile Gln	Asp Leu Leu Gln Val	15 Met Arg Thr Glu Pro	Lys His Tyr Val 80 Leu
Pro 20 Leu 35 Leu 65 Gln 85 Gln 100 Ala	Pro Arg Tyr Pro Gly Arg	Leu Gly Leu Gln Thr Tyr Leu	Ala Ala Pro Gly Asn Val Arg	Ala 5 Ala Ala Cys Ala Leu Ile	Ser 25 Ser 40 Gln 55 Ser 70 Ile 90 Val	Thr Pro Val Leu Ala Arg	Gln Glu Val Ser His Gly	Val Thr Gln Phe Asn Thr	10 Cys His Gly Leu Gln Gln	Thr 30 Leu 45 Asn 60 Gln 75 Val 95 Leu 110	Gly Asp Leu Asp Arg Phe	Thr Met Glu Gln Glu	Asp Leu Gln Val Asp	15 Met Arg Thr Glu Pro Asn	Lys His Tyr Val 80 Leu Tyr
Pro 20 Leu 35 Leu 65 Gln 100 Ala 115 Val	Pro Arg Tyr Pro Gly Arg Leu	Leu Gly Leu Gln Thr Tyr Leu Ala	Ala Ala Pro Gly Asn Val Arg Val	Ala 5 Ala Ala Cys Ala Leu Ile	Ser 25 Ser 40 Gln 55 Ser 70 Ile 90 Val 105 Asp	Thr Pro Val Leu Ala Arg Asn	Gln Glu Val Ser His Gly Gly	Val Thr Gln Phe Asn Thr Asp	10 Cys His Gly Leu Gln Gln Pro	Thr 30 Leu 45 Asn 60 Gln 75 Val 95 Leu 110 Leu 125	Gly Asp Leu Asp Arg Phe Asn	Thr Met Glu Ile Gln Glu Asn	Asp Leu Gln Val Asp Thr	15 Met Arg Thr Glu Pro Asn Thr	Lys His Tyr Val 80 Leu Tyr Pro
Pro 20 Leu 35 Leu 65 Gln 100 Ala 115 Val 130	Pro Arg Tyr Pro Gly Arg Leu Thr	Leu Gly Leu Gln Thr Tyr Leu Ala Gly	Ala Ala Pro Gly Asn Val Arg Val Ala	Ala 5 Ala Cys Ala Leu Ile Leu Ser	Ser 25 Ser 40 Gln 55 Ser 70 Ile 90 Val 105 Asp 120 Pro	Thr Pro Val Leu Ala Arg Asn Gly	Gln Glu Val Ser His Gly Gly	Val Thr Gln Phe Asn Thr Asp Leu	10 Cys Gly Leu Gln Gln Pro Arg	Thr 30 Leu 45 Asn 60 Gln 75 Val 95 Leu 110 Leu 125 Glu 140	Gly Asp Leu Asp Arg Phe Asn Leu	Thr Met Glu Ile Gln Glu Asn Gln	Asp Leu Gln Val Asp Thr Leu	15 Met Arg Thr Glu Pro Asn Thr Arg	Lys His Tyr Val 80 Leu Tyr Prc Ser Glr.
Pro 20 Leu 35 Leu 65 Gln 100 Ala 115 Val 130 Leu 145	Pro Arg Tyr Pro Gly Arg Leu Thr	Leu Gly Leu Gln Thr Tyr Leu Ala Gly Glu	Ala Ala Pro Gly Asn Val Arg Val Ala Ile	Ala 5 Ala Cys Ala Leu Leu Ser Leu	Ser 25 Ser 40 Gln 55 Ser 70 Ile 90 Val 105 Asp 120 Pro 135 Lys	Thr Pro Val Leu Ala Arg Gly Gly	Gln Glu Val Ser His Gly Gly Gly	Val Thr Gln Phe Asn Thr Asp Leu Val	10 Cys Gly Leu Gln Gln Pro Arg Leu	Thr 30 Leu 45 Asn 60 Gln 75 Val 95 Leu 110 Leu 125 Glu 140 Ile 155	Gly Asp Leu Asp Arg Phe Asn Leu Gln	Thr Met Glu Ile Gln Glu Asn Gln Arg	Asp Leu Gln Val Asp Thr Leu Asn	15 Met Arg Thr Glu Pro Asn Thr Arg Pro	Lys His Tyr Val Leu Tyr Pro Ser Gln 160

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His 195	Pro	Cys	Ser	Pro	Met 200	Суз	Lys	Gly	Ser	Arg 205	Сүз	Trp	Gly	Glu	Ser
Ser 210	Glu	Aab	Сүз	Gln	Ser 215	Leu	Thr	Arg	Thr	Val 220	Сүз	Ala	Gly	Gly	Суз
Ala 225	Arg	Суа	Lys	Gly	Pro 230	Leu	Pro	Thr	Asp	Суз 235	Суа	His	Glu	Gln	Cys 240
Ala 245	Ala	Gly	Суз	Thr	Gly 250	Pro	Lys	His	Ser	Asp 255	Суз	Leu	Ala	Cys	Leu
His 260	Phe	Asn	His	Ser	Gly 265	Ile	Суз	Glu	Leu	His 270	Суз	Pro	Ala	Leu	Val
Thr 275	Tyr	Asn	Thr	Asp	Thr 280	Phe	Glu	Ser	Met	Pro 285	Asn	Pro	Glu	Gly	Arg
Tyr 290	Thr	Phe	Gly	Ala	Ser 295	СЛа	Val	Thr	Ala	Сув 300	Pro	Tyr	Asn	Tyr	Leu
Ser 305	Thr	Asp	Val	Gly	Ser 310	Сүз	Thr	Leu	Val	Cys 315	Pro	Leu	His	Asn	Gln 320
Glu 325	Val	Thr	Ala	Glu	Asp 330	Gly	Thr	Gln	Arg	Суя 335	Glu	ГЛа	Суз	Ser	Lys
Pro 340	Cys	Ala	Arg	Val	Суз 345	Tyr	Gly	Leu	Gly	Met 350	Glu	His	Leu	Arg	Glu
Val 355	Arg	Ala	Val	Thr	Ser 360	Ala	Asn	Ile	Gln	Glu 365	Phe	Ala	Gly	Cys	Lys
Lуя 370	Ile	Phe	Gly	Ser	Leu 375	Ala	Phe	Leu	Pro	Glu 380	Ser	Phe	Asp	Gly	Asp
Pro 385	Ala	Ser	Asn	Thr	Ala 390	Pro	Leu	Gln	Pro	Glu 395	Gln	Leu	Gln	Val	Phe 400
Glu 405	Thr	Leu	Glu	Glu	Ile 410	Thr	Gly	Tyr	Leu	Tyr 415	Ile	Ser	Ala	Trp	Pro
Asp 420	Ser	Leu	Pro	Asp	Leu 425	Ser	Val	Phe	Gln	Asn 430	Leu	Gln	Val	Ile	Arg
Gly 435	Arg	Ile	Leu	His	Asn 440	Gly	Ala	Tyr	Ser	Leu 445	Thr	Leu	Gln	Gly	Leu
Gly 450	Ile	Ser	Trp	Leu	Gly 455	Leu	Arg	Ser	Leu	Arg 460	Glu	Leu	Gly	Ser	Gly
Leu 465	Ala	Leu	Ile	His	His 470	Asn	Thr	His	Leu	Cys 475	Phe	Val	His	Thr	Val 480
	Trp	Asp	Gln	Leu		Arg	Asn	Pro	His		Ala	Leu	Leu	His	
	Asn	Arg	Pro	Glu		Glu	Суз	Val	Gly		Gly	Leu	Ala	Cys	His
	Leu	Суз	Ala	Arg		His	Суз	Trp	Gly		Gly	Pro	Thr	Gln	Cys
	Asn	Суз	Ser	Gln		Leu	Arg	Gly	Gln		Суз	Val	Glu	Glu	Cys
	Val	Leu	Gln	Gly		Pro	Arg	Glu	Tyr		Asn	Ala	Arg	His	Cys 560
	Pro	Суз	His	Pro		Суз	Gln	Pro	Gln		Gly	Ser	Val	Thr	
Phe	Gly	Pro	Glu	Ala	Asp	Gln	Суз	Val	Ala	Суз	Ala	His	Tyr	Lys	Asp
580					585					590					

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Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile Ile Ser <210> SEQ ID NO 243 <211> LENGTH: 647 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 243 Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gl<br/>n $\operatorname{Arg}$  As<br/>n $\operatorname{Pro}$ Gln Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val 

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Thr 275	Tyr	Asn	Thr	Asp	Thr 280	Phe	Glu	Ser	Met	Pro 285	Asn	Pro	Glu	Gly	Arg	
Tyr 290	Thr	Phe	Gly	Ala	Ser 295	Суз	Val	Thr	Ala	Сув 300	Pro	Tyr	Asn	Tyr	Leu	
Ser 305	Thr	Asp	Val	Gly	Ser 310	Сүв	Thr	Leu	Val	Cys 315	Pro	Leu	His	Asn	Gln 320	
Glu 325	Val	Thr	Ala	Glu	Asp 330	Gly	Thr	Gln	Arg	Сув 335	Glu	Lys	Сүз	Ser	Lys	
Pro 340	Cys	Ala	Arg	Val	Cys 345	Tyr	Gly	Leu	Gly	Met 350	Glu	His	Leu	Arg	Glu	
Val 355	Arg	Ala	Val	Thr	Ser 360	Ala	Asn	Ile	Gln	Glu 365	Phe	Ala	Gly	Суз	Lys	
Lys 370	Ile	Phe	Gly	Ser	Leu 375	Ala	Phe	Leu	Pro	Glu 380	Ser	Phe	Asp	Gly	Asp	
Pro 385	Ala	Ser	Asn	Thr	Ala 390	Pro	Leu	Gln	Pro	Glu 395	Gln	Leu	Gln	Val	Phe 400	
Glu 405	Thr	Leu	Glu	Glu	Ile 410	Thr	Gly	Tyr	Leu	Tyr 415	Ile	Ser	Ala	Trp	Pro	
Asp 420	Ser	Leu	Pro	Asp	Leu 425	Ser	Val	Phe	Gln	Asn 430	Leu	Gln	Val	Ile	Arg	
Gly 435	Arg	Ile	Leu	His	Asn 440	Gly	Ala	Tyr	Ser	Leu 445	Thr	Leu	Gln	Gly	Leu	
Gly 450	Ile	Ser	Trp	Leu	Gly 455	Leu	Arg	Ser	Leu	Arg 460	Glu	Leu	Gly	Ser	Gly	
Leu 465	Ala	Leu	Ile	His	His 470	Asn	Thr	His	Leu	Cys 475	Phe	Val	His	Thr	Val 480	
Pro 485	Trp	Asp	Gln	Leu	Phe 490	Arg	Asn	Pro	His	Gln 495	Ala	Leu	Leu	His	Thr	
Ala 500	Asn	Arg	Pro	Glu	Asp 505	Glu	Cys	Val	Gly	Glu 510	Gly	Leu	Ala	Суз	His	
Gln 515	Leu	Cys	Ala	Arg	Gly 520	His	Сув	Trp	Gly	Pro 525	Gly	Pro	Thr	Gln	Сув	
Val 530	Asn	Cys	Ser	Gln	Phe 535	Leu	Arg	Gly	Gln	Glu 540	Сүз	Val	Glu	Glu	Сув	
Arg 545	Val	Leu	Gln	Gly	Leu 550	Pro	Arg	Glu	Tyr	Val 555	Asn	Ala	Arg	His	Cys 560	
Leu 565	Pro	Сув	His	Pro	Glu 570	Сув	Gln	Pro	Gln	Asn 575	Gly	Ser	Val	Thr	Суз	
Phe 580	Gly	Pro	Glu	Ala	Asp 585	Gln	Cys	Val	Ala	Cys 590	Ala	His	Tyr	Lys	Asp	
Pro 595	Pro	Phe	Суз	Val	Ala 600	Arg	Cys	Pro	Ser	Gly 605	Val	Lys	Pro	Asp	Leu	
Ser 610	Tyr	Met	Pro	Ile	Trp 615	Lys	Phe	Pro	Asp	Glu 620	Glu	Gly	Ala	Cys	Gln	
Pro 625	Cys	Pro	Ile	Asn	Суз 630	Thr	His	Ser	Cys	Val 635	Asp	Leu	Asp	Asp	Lys 640	
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Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu 245 250 255											
His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val 260 265 270											
Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg275280285											
Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu 290 295 300											
Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln 305 310 315 320											
Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys 325 330 335											
Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu 340 345 350											
Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys 355 360 365											

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Lys Ile Phe Gly 370	Ser Leu A 375	la Phe Leu	Pro Glu S 380	Ser Phe	Asp Gly	Asp
Pro Ala Ser Asn 385	Thr Ala P: 390	ro Leu Glr	ı Pro Glu ( 395	Gln Leu	Gln Val	Phe 400
Glu Thr Leu Glu 405	Glu Ile T 410	hr Gly Tyr	Leu Tyr 1 415	Ile Ser	Ala Trp	Pro
Asp Ser Leu Pro 420	Asp Leu S 425	er Val Phe	Gln Asn 1 430	Leu Gln	Val Ile	Arg
Gly Arg Ile Leu 435	His Asn G 440	ly Ala Tyr	Ser Leu 5 445	Thr Leu	Gln Gly	Leu
Gly Ile Ser Trp 450	Leu Gly Lo 455	eu Arg Ser	Leu Arg ( 460	Glu Leu	Gly Ser	Gly
Leu Ala Leu Ile 465	His His A 470	sn Thr His	Leu Cys I 475	Phe Val	His Thr	Val 480
Pro Trp Asp Gln 485	Leu Phe A: 490	rg Asn Pro	His Gln 4 495	Ala Leu	Leu His	Thr
Ala Asn Arg Pro 500	Glu Asp G 505	lu Cys Val	. Gly Glu ( 510	Gly Leu	Ala Cys	His
Gln Leu Cys Ala 515	Arg Gly H 520	is Cys Trp	Gly Pro ( 525	Gly Pro	Thr Gln	Суз
Val Asn Cys Ser 530	Gln Phe Lo 535	eu Arg Gly	Gln Glu ( 540	Cys Val	Glu Glu	Суз
Arg Val Leu Gln 545	Gly Leu P: 550	ro Arg Glu	Tyr Val 2 555	Asn Ala	Arg His	Суз 560
Leu Pro Cys His 565	Pro Glu C 570	ys Gln Pro	Gln Asn ( 575	Gly Ser	Val Thr	Суз
Phe Gly Pro Glu 580	Ala Asp G 585	ln Cys Val	. Ala Cys A 590	Ala His	Tyr Lys	Asp
Pro Pro Phe Cys 595	Val Ala A:	rg				
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Pro Pro Gly Ala 20	Ala Ser Ti 25	hr Gln Val	. Cys Thr ( 30	Gly Thr	Asp Met	Lys
Leu Arg Leu Pro 35	Ala Ser P: 40	ro Glu Thr	His Leu A 45	Asp Met	Leu Arg	His
Leu Tyr Gln Gly 50	Cys Gln V 55	al Val Glr	Gly Asn 1 60	Leu Glu	Leu Thr	Tyr
Leu Pro Thr Asn 65	Ala Ser Lo 70	eu Ser Phe	ELEU Gln 2 75	Asp Ile	Gln Glu	Val 80
Gln Gly Tyr Val 85	Leu Ile A 90	la His Asr	ı Gln Val 2 95	Arg Gln	Val Pro	Leu

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Gln 100	Arg	Leu	Arg	Ile	Val 105	Arg	Gly	Thr	Gln	Leu 110	Phe	Glu	Asp	Asn	Tyr					
Ala 115	Leu	Ala	Val	Leu	Asp 120	Asn	Gly	Asp	Pro	Leu 125	Asn	Asn	Thr	Thr	Pro					
Val 130	Thr	Gly	Ala	Ser	Pro 135	Gly	Gly	Leu	Arg	Glu 140	Leu	Gln	Leu	Arg	Ser					
Leu 145	Thr	Glu	Ile	Leu	Lys 150	Gly	Gly	Val	Leu	Ile 155	Gln	Arg	Asn	Pro	Gln 160					
Leu 165	Сув	Tyr	Gln	Asp	Thr 170	Ile	Leu	Trp	ГЛа	Asp 175	Ile	Phe	His	Гла	Asn					
Asn 180	Gln	Leu	Ala	Leu	Thr 185	Leu	Ile	Asp	Thr	Asn 190	Arg	Ser	Arg	Ala	Суа					
His 195	Pro	Сув	Ser	Pro	Met 200	Сүз	Lys	Gly	Ser	Arg 205	Суз	Trp	Gly	Glu	Ser					
Ser 210	Glu	Asp	Суз	Gln	Ser 215	Leu	Thr	Arg	Thr	Val 220	Cys	Ala	Gly	Gly	Суз					
Ala 225	Arg	Суз	Lys	Gly	Pro 230	Leu	Pro	Thr	Asp	Cys 235	Суз	His	Glu	Gln	Cys 240					
	Ala	Gly	Суз	Thr		Pro	Гла	His	Ser		Суз	Leu	Ala	Суз						
	Phe	Asn	His	Ser		Ile	Суз	Glu	Leu		Суз	Pro	Ala	Leu	Val					
Thr 275	Tyr	Asn	Thr	Asp	Thr 280	Phe	Glu	Ser	Met	Pro 285	Asn	Pro	Glu	Gly	Arg					
Tyr 290	Thr	Phe	Gly	Ala	Ser 295	Суз	Val	Thr	Ala	Суз 300	Pro	Tyr	Asn	Tyr	Leu					
Ser 305	Thr	Asp	Val	Gly	Ser 310	Сүз	Thr	Leu	Val	Cys 315	Pro	Leu	His	Asn	Gln 320					
Glu 325	Val	Thr	Ala	Glu	Asp 330	Gly	Thr	Gln	Arg	Cys 335	Glu	Lys	Суз	Ser	Lys					
Pro	Сув																			
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Pro 20	Pro	Gly	Ala	Ala	Ser 25	Thr	Gln	Val	Сув	Thr 30	Gly	Thr	Asp	Met	Lys					
Leu 35	Arg	Leu	Pro	Ala	Ser 40	Pro	Glu	Thr	His	Leu 45	Asp	Met	Leu	Arg	His					
Leu 50	Tyr	Gln	Gly	Суз	Gln 55	Val	Val	Gln	Gly	Asn 60	Leu	Glu	Leu	Thr	Tyr					
Leu 65	Pro	Thr	Asn	Ala	Ser 70	Leu	Ser	Phe	Leu	Gln 75	Asp	Ile	Gln	Glu	Val 80					
Gln 85	Gly	Tyr	Val	Leu	Ile 90	Ala	His	Asn	Gln	Val 95	Arg	Gln	Val	Pro	Leu					
Gln 100	Arg	Leu	Arg	Ile	Val 105	Arg	Gly	Thr	Gln	Leu 110	Phe	Glu	Asp	Asn	Tyr					

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Ala 115	Leu	Ala	Val	Leu	Asp 120	Asn	Gly	Asp	Pro	Leu 125	Asn	Asn	Thr	Thr	Pro
Val 130	Thr	Gly	Ala	Ser	Pro 135	Gly	Gly	Leu	Arg	Glu 140	Leu	Gln	Leu	Arg	Ser
Leu 145	Thr	Glu	Ile	Leu	Lys 150	Gly	Gly	Val	Leu	Ile 155	Gln	Arg	Asn	Pro	Gln 160
Leu 165	Cys	Tyr	Gln	Asp	Thr 170	Ile	Leu	Trp	Lys	Asp 175	Ile	Phe	His	Lys	Asn
Asn 180	Gln	Leu	Ala	Leu	Thr 185	Leu	Ile	Asp	Thr	Asn 190	Arg	Ser	Arg	Ala	Cys
His 195	Pro	Cys	Ser	Pro	Met 200	Сув	Lys	Gly	Ser		Сув	Trp	Gly	Glu	Ser
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Ala	Arg	Cys	Lys	Gly	Pro	Leu	Pro	Thr	Asp	Cys	Суз	His	Glu	Gln	-
	Ala	Gly	Суз	Thr	230 Gly	Pro	Lys	His	Ser	-	Суз	Leu	Ala	Суз	240 Leu
	Phe	Asn	His	Ser	250 Gly	Ile	Суз	Glu	Leu		Cys	Pro	Ala	Leu	Val
260 Thr	Tyr	Asn	Thr	Asp	265 Thr	Phe	Glu	Ser	Met	270 Pro	Asn	Pro	Glu	Gly	Arg
275 Tvr	Thr	Phe	Glv	Ala	280 Ser	Cvs	Val	Thr	Ala	285 Cvs	Pro	Tvr	Asn	Tvr	Leu
290			-		295 Ser	-				300		-		-	
305		-		-	310	-				315					320
325					Asp 330	-			-	335		-	-		-
Pro 340	Cys	Ala	Arg	Val	Суз 345	Tyr	Gly	Leu	Gly	Met 350	Glu	His	Leu	Arg	Glu
Val 355	Arg	Ala	Val	Thr	Ser 360	Ala	Asn	Ile	Gln	Glu 365	Phe	Ala	Gly	Сүз	ГЛЗ
Lys 370	Ile	Phe	Gly	Ser	Leu 375	Ala	Phe	Leu	Pro	Glu 380	Ser	Phe	Asp	Gly	Asp
Pro 385	Ala	Ser	Asn	Thr	Ala 390		Leu	Gln	Pro	Glu 395	Gln	Leu	Gln	Val	Phe 400
Glu 405	Thr	Leu	Glu	Glu	Ile 410	Thr	Gly	Tyr	Leu	Tyr 415	Ile	Ser	Ala	Trp	Pro
Asp 420	Ser	Leu	Pro	Asp	Leu 425	Ser	Val	Phe	Gln	Asn 430	Leu	Gln	Val	Ile	Arg
Gly 435	Arg	Ile	Leu	His	Asn 440	Gly	Ala	Tyr	Ser	Leu 445	Thr	Leu	Gln	Gly	Leu
Gly 450	Ile	Ser	Trp	Leu	Gly 455	Leu	Arg	Ser	Leu	Arg 460	Glu	Leu	Gly	Ser	Gly
	Ala	Leu	Ile	His	His 470	Asn	Thr	His	Leu	Cys 475	Phe	Val	His	Thr	Val 480
	Trp	Asp	Gln	Leu	Phe 490	Arg	Asn	Pro	His		Ala	Leu	Leu	His	
Ala	Asn	Arg	Pro	Glu	Asp	Glu	Cys	Val	Gly	Glu	Gly	Leu	Ala	Суз	His
500 Gln	Leu	Суз	Ala	Arg	505 Gly	His	Сув	Trp	Gly	510 Pro	Gly	Pro	Thr	Gln	Суз

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Val 530	Asn	СЛа	Ser	Gln	Phe 535	Leu	Arg	Gly	Gln	Glu 540	Суа	Val	Glu	Glu	Суа
Arg 545	Val	Leu	Gln	Gly	Leu 550	Pro	Arg	Glu	Tyr	Val 555	Asn	Ala	Arg	His	Cys 560
Leu 565	Pro	Cys	His	Pro	Glu 570	Сүз	Gln	Pro	Gln	Asn 575	Gly	Ser	Val	Thr	Суз
Phe 580	Gly	Pro	Glu	Ala	Asp 585	Gln	Сүз	Val	Ala	Cys 590	Ala	His	Tyr	Lys	Asp
Pro 595	Pro	Phe	Сүв	Val	Ala 600	Arg	Сүз	Pro	Ser	Gly 605	Val	Гла	Pro	Asp	Leu
Ser 610	Tyr	Met	Pro	Ile	Trp 615	Lys	Phe	Pro	Asp	Glu 620	Glu	Gly	Ala	Суз	Gln
Pro 625	Суз	Pro	Ile	Asn	Суз 630	Thr	His	Ser	Сув	Val 635	Asp	Leu	Asp	Asp	Lys 640
Gly 645	Суз	Pro	Ala	Glu	Gln 650	Arg	Ala	Ser	Pro	Leu 655	Thr	Ser	Ile	Ile	Ser
Ala 660	Val	Val	Gly	Ile	Leu 665	Leu	Val	Val	Val	Leu 670	Gly	Val	Val	Phe	Gly
Ile 675	Leu	Ile	Lys	Arg	Arg 680	Gln	Gln	Lys	Ile	Arg 685	Lys	Tyr	Thr	Met	Arg
Arg 690	Leu	Leu	Gln	Glu	Thr 695	Glu	Leu	Val	Glu	Pro 700	Leu	Thr	Pro	Ser	Gly
Ala 705	Met	Pro	Asn	Gln	Ala 710	Gln	Met	Arg	Ile	Leu 715	LYa	Glu	Thr	Glu	Leu 720
Arg 725	Lys	Val	Lys	Val	Leu 730	Gly	Ser	Gly	Ala	Phe 735	Gly	Thr	Val	Tyr	Lys
Gly 740	Ile	Trp	Ile	Pro	Asp 745	Gly	Glu	Asn	Val	Lys 750	Ile	Pro	Val	Ala	Ile
Lys 755	Val	Leu	Arg	Glu	Asn 760	Thr	Ser	Pro	Lys	Ala 765	Asn	Lys	Glu	Ile	Leu
Asp 770	Glu	Ala	Tyr	Val	Met 775	Ala	Gly	Val	Gly	Ser 780	Pro	Tyr	Val	Ser	Arg
Leu 785	Leu	Gly	Ile	СЛа	Leu 790	Thr	Ser	Thr	Val	Gln 795	Leu	Val	Thr	Gln	Leu 800
Met 805	Pro	Tyr	Gly	Сүз	Leu 810	Leu	Asp	His	Val	Arg 815	Glu	Asn	Arg	Gly	Arg
Leu 820	Gly	Ser	Gln	Asp	Leu 825	Leu	Asn	Trp	Сүз	Met 830	Gln	Ile	Ala	Lys	Gly
Met 835	Ser	Tyr	Leu	Glu	Asp 840	Val	Arg	Leu	Val	His 845	Arg	Asp	Leu	Ala	Ala
Arg 850	Asn	Val	Leu	Val	Lys 855	Ser	Pro	Asn	His	Val 860	Гла	Ile	Thr	Asp	Phe
Gly 865	Leu	Ala	Arg	Leu	Leu 870	Asp	Ile	Asp	Glu	Thr 875	Glu	Tyr	His	Ala	Asp 880
Gly 885	Gly	Lys	Val	Pro	Ile 890	Lys	Trp	Met	Ala	Leu 895	Glu	Ser	Ile	Leu	Arg
Arg 900	Arg	Phe	Thr	His	Gln 905	Ser	Asp	Val	Trp	Ser 910	Tyr	Gly	Val	Thr	Val
Trp 915	Glu	Leu	Met	Thr	Phe 920	Gly	Ala	Lys	Pro	Tyr 925	Asp	Gly	Ile	Pro	Ala

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Arg Glu : 930		Leu Leu Glu L 935		lu Arg Leu Pro Gln Pro 40
Pro Ile ( 945	-	Asp Val Tyr M 950		et Val Lys Cys Trp Met 55 960
Ile Asp & 965	-	Arg Pro Arg P 970	-	lu Leu Val Ser Glu Phe 75
Ser Arg 1 980	-	Asp Pro Gln A 985		al Val Ile Gln Asn Glu 90
Asp Leu ( 995		Ser Pro Leu 1000		Thr Phe Tyr Arg Ser Leu 1005
Leu Glu 1010	Yab Yab Yab	Met Gly Asp 1015	Leu Val	Asp Ala Glu Glu Tyr 1020
Leu Val 1025	Pro Gln Gln	Gly Phe Phe 1030	Cys Pro	Asp Pro Ala Pro Gly 1035
Ala Gly 1040	Gly Met Val	His His Arg 1045	His Arg	Ser Ser Ser Thr Arg 1050
Ser Gly 1055	Gly Gly Asp	Leu Thr Leu 1060	Gly Leu	Glu Pro Ser Glu Glu 1065
Glu Ala 1070	Pro Arg Ser	Pro Leu Ala 1075	Pro Ser	Glu Gly Ala Gly Ser 1080
Asp Val 1085	Phe Asp Gly	Asp Leu Gly 1090	Met Gly	Ala Ala Lys Gly Leu 1095
Gln Ser 1100	Leu Pro Thr	His Asp Pro 1105	Ser Pro	Leu Gln Arg Tyr Ser 1110
Glu Asp 1115	Pro Thr Val	Pro Leu Pro 1120	Ser Glu	Thr Asp Gly Tyr Val 1125
Ala Pro 1130	Leu Thr Cys	Ser Pro Gln 1135	Pro Glu	Tyr Val Asn Gln Pro 1140
Asp Val 1145	Arg Pro Gln	Pro Pro Ser 1150	Pro Arg	Glu Gly Pro Leu Pro 1155
Ala Ala 1160	Arg Pro Ala	Gly Ala Thr 1165	Leu Glu	Arg Pro Lys Thr Leu 1170
Ser Pro 1175	Gly Lys Asn	Gly Val Val 1180	Гла Уар	Val Phe Ala Phe Gly 1185
Gly Ala 1190	Val Glu Asn	Pro Glu Tyr 1195	Leu Thr	Pro Gln Gly Gly Ala 1200
Ala Pro 1205	Gln Pro His	Pro Pro Pro 1210	Ala Phe	Ser Pro Ala Phe Asp 1215
Asn Leu 1220	Tyr Tyr Trp	Asp Gln Asp 1225	Pro Pro	Glu Arg Gly Ala Pro 1230
Pro Ser 1235	Thr Phe Lys	Gly Thr Pro 1240	Thr Ala	Glu Asn Pro Glu Tyr 1245
Leu Gly 1250	Leu Asp Val	Pro Val 1255		
<pre>&lt;211&gt; LEM &lt;212&gt; TYM &lt;213&gt; ORC &lt;220&gt; FEM &lt;221&gt; NAM &lt;223&gt; OTH</pre>	PE: DNA GANISM: Arti: ATURE: ME/KEY: sour	ION: /note="D		on of Artificial Sequence:

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Ser Leu 20	Arg	Leu	Ser	Сув 25	Ala	Ala	Ser	Gly	Phe 30	Thr	Phe	Ser	Ser	Tyr
Ser Met 35	Asn	Trp	Val	Arg 40	Gln	Ala	Pro	Gly	Lys 45	Gly	Leu	Glu	Trp	Val
Ser Ser 50	Ile	Ser	Ser	Ser 55	Ser	Ser	Tyr	Ile	Tyr 60	Tyr	Ala	Asp	Ser	Val
Lys Gly 65	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ala 75	ГЛа	Asn	Ser	Leu	Tyr 80
Leu Gln 85	Met	Asn	Ser	Leu 90	Arg	Ala	Glu	Asp	Thr 95	Ala	Val	Tyr	Tyr	Суз
Ala Arg														
	ENGTI YPE : RGANI EATUI AME/I THER YNTH	H: 98 PRT ISM: RE: KEY: INFC etic]	Art: sour DRMA poly	rce	: /nc	-		ript	ion	of Z	Artif	Ēicia	al Se	quen
<400> SI														
Glu Val 1			5					10					15	
Ser Leu 20	Arg	Leu	Ser	Сув 25	Ala	Ala	Ser	Gly	Phe 30	Thr	Phe	Ser	Ser	Tyr
Ser Met 35	Asn	Trp	Val	Arg 40	Gln	Ala	Pro	Gly	Lys 45	Gly	Leu	Glu	Trp	Val
Ser Tyr 50	Ile	Ser	Ser	Ser 55	Ser	Ser	Thr	Ile	Tyr 60	Tyr	Ala	Asp	Ser	Val
Lys Gly 65	Arg	Phe	Thr	Ile 70	Ser	Arg	Aab	Asn	Ala 75	LÀa	Asn	Ser	Leu	Tyr 80
Leu Gln 85	Met	Asn	Ser	Leu 90	Arg	Asb	Glu	Asp	Thr 95	Ala	Val	Tyr	Tyr	Суа
Ala Arg														
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Ser Leu 20	Arg	Leu	Ser	Суз 25	Ala	Ala	Ser	Gly	Phe 30	Thr	Phe	Ser	Ser	Tyr
Gly Met 35	His	Trp	Val	Arg 40	Gln	Ala	Pro	Gly	Lys 45	Gly	Leu	Glu	Trp	Val
Ala Val 50	Ile	Trp	Tyr	Asp 55	Gly	Ser	Asn	ГЛа	Tyr 60	Tyr	Ala	Asp	Ser	Val
Lys Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	ГЛа	Asn	Thr	Leu	Tyr

65 70 75 80 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Arg <210> SEQ ID NO 262 <211> LENGTH: 98 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 262 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg 5 10 15 1 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr 25 20 30 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45 Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val 55 60 50 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Lys <210> SEQ ID NO 263 <211> LENGTH: 98 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 263 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala 1 5 10 15 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr 20 25 30 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 40 45 35 Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe 50 55 60 Gln Gly Trp Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr 70 75 65 80 Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys 90 85 95 Ala Arg <210> SEQ ID NO 264 <211> LENGTH: 92 <212> TYPE: PRT

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Ile Tyr Asn Asn Asp Gln Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser 50 55 60 Gly Ser Lys Ser Gly Thr Ser Gly Ser Leu Val Ile Ser Gly Leu Gln 75 65 70 80 Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Trp Asp Asp Ser Leu 85 90 95 Asn Gly Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ala 100 105 110 <210> SEQ ID NO 267 <211> LENGTH: 94 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 267 Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly 10 Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser 20 30 Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr 35 45 40 Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe 50 55 60 Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala 70 65 75 80 Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met 90 85 <210> SEO ID NO 268 <211> LENGTH: 93 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 268 Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys 15 1 5 10 Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Asn 25 30 20 Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr Val 35 40 45 Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser 50 55 60 Gly Ser Ile Asp Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly Leu Lys 70 75 Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp 85 90 <210> SEQ ID NO 269 <211> LENGTH: 91 <212> TYPE: PRT

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Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe 55 60 50 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu 65 70 75 80 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr 85 90 <210> SEQ ID NO 272 <211> LENGTH: 94 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 272 Gln Ser Ala Leu Thr Gln Pro Pro Ser Ala Ser Gly Ser Pro Gly Gln 10 1 5 15 Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr 25 20 30 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu 35 40 45 Met Ile Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe 50 55 60 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Val Ser Gly Leu 70 75 80 65 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala 85 90 <210> SEQ ID NO 273 <211> LENGTH: 94 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <221> NAME/KEY: source <223> OTHER INFORMATION: /note="Description of Artificial Sequence: Syntheticpolypeptide" <400> SEQUENCE: 273 Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln 5 10 1 15 Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly 20 25 30 Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu 35 40 45 Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe 55 50 60 Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu 70 65 75 80 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp 90 85 <210> SEQ ID NO 274 <211> LENGTH: 93 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE:

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**1**. A binding protein that specifically binds ErbB2, wherein the binding protein is an ErbB2 agonist.

**2**. The binding protein of claim **1** which reduces cellular proliferation in an ErbB2-expressing cancer cell.

**3**. The binding protein of claim **1** which increases apoptosis in an ErbB2-expressing tumor.

**4**. The binding protein of claim **1** which reduces the growth of an ErbB2-expressing tumor.

5. The binding protein of claim 2 wherein the ErbB2expressing cancer cell is a breast cancer cell.

**6**. The binding protein of claim **2** wherein the ErbB2 expressing cancer cell is from a cell line selected from the group consisting of: SKBR3, BT474, MDA-MB-453 and MDA-MB-361.

7. A binding protein that specifically binds ErbB2, wherein the binding protein preferentially binds an ErbB2 extracellular domain (ECD) homo-dimer over ErbB2 ECD monomer and shed ErbB2 ECD.

**8**. The binding protein of claim **1**, wherein the binding protein preferentially binds an ErbB2 extracellular domain (ECD) homo-dimer over ErbB2 ECD monomer and shed ErbB2 ECD.

**9**. The binding protein of claim **2**, that possesses one or more or the following properties:

- (a) increases ErbB2 phosphorylation in a breast cancer cell;
- (b) increases the phosphorylation of one or more of AKT, MAPK and ERK; or
- (c) binds ErbB2 ECD in the CR2 domain.

**10**. The binding protein of claim **1** which is an antibody, an antigen-binding fragment of an antibody or a small modular immunopharmaceutical (SMIP).

11. The binding protein of claim 10 which is an antigenbinding fragment of an antibody, wherein the antigen-binding fragment is selected from the group consisting of: a Fab fragment, an F(ab')2 fragment, an scFv, a dAb, and Fv fragment and a VHH.

**12**. The binding protein of claim **1**, which is human antibody or an antigen-binding fragment thereof.

**13**. The binding protein of claim **1**, wherein the ErbB2 is human ErbB2 (SEQ ID NO: 246).

**14**. A binding protein that specifically binds ErbB2, wherein the binding protein comprises:

- (a) a VH domain comprising the CDR1, CDR2 and CDR3 amino acid sequences set forth in any one of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 65 or 67; or
- (b) a VL domain comprising the CDR1, CDR2 and CDR3 amino acid sequences set forth in any one of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 63, 64, 66, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94 or 95; or
- (c) a VH of (a) and a VL of (b).

**15**. The binding protein of claim **14**, comprising the VH CDR1, CDR2 and CDR3 amino acid sequences and the VL CDR1, CDR2 and CDR3 sequences of any one of: S1R2A_CS_1F7, S1R2A_CS_1D1, S1R2C_CS_1D3, S1R3D2_BMV_1E1, S1R3C1_CS_1D3, S1R3B2_DP47_1E8, S1R3B2_BMV_1G2, S1R3B2_BMV_1H5, S1R3C1_CS_46, S1R3B2_DP47_1C9, S1R3B2_DP47_1E10, S1R3C1_CS_1B10,

S1R3A1_BMV_1F3, S1R3B1_BMV_1G11, S1R3A1_ BMV_1G4, S1R3B1_BMV_1H11, S1R3A1_CS_1B9, S1R3B1_BMV_1H9, S1R3A1_CS_1B10, S1R3B1_ BMV_1C12, S1R3C1_BMV_1H11, S1R3B1_BMV_ 1A10, S1R3A1_CS_1D11, S1R3C1_DP47_1H1, S1R3A1_CS_1B12, S1R3B1_BMV_1H5, S1R3A1_

DP47_1A6, S1R3B1_DP47_1E1 or S1R3B1_BMV_1A1. **16**. A binding protein that specifically binds ErbB2, wherein the binding protein comprises:

- (a) a VH having the amino acid sequence that is at least 90% identical to any one of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 65 or 67; or
- (b) a VL having the amino acid sequence that is at least 90% identical to any one of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 63, 64, 66, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94 or 95;
- (c) a VH of (a) and a VL of (b); or
- (d) a VH and a VL amino acid sequence that are at least 90% identical to the VH and VL, amino acid sequences, respectively, in any one of S1R2A_CS_1F7, S1R2A_ CS_1D11, S1R2C_CS_1D3, S1R2C_CS_1H12, S1R2A_CS_1D3, S1R3B2_BMV_1E1, S1R3C1_ CS_1D3, S1R3B2_DP47_1E8, S1R3B2_BMV_1G2, S1R3B2_BMV_1H5, S1R3C1_CS_1A6, S1R3B2_ DP47_1C9, S1R3B2_DP47_1E10, S1R3C1_CS_ 1B10, S1R3A1_BMV_1F3, S1R3B1_BMV_1G11, S1R3A1_BMV_1G4, S1R3B1_BMV_1H11, S1R3A1_CS_1B9, S1R3B1_BMV_1H9, S1R3A1_ CS_1B10, S1R3B1_BMV_1C12, S1R3C1_BMV_ 1H11, S1R3B1_BMV_1A10, S1R3A1_CS_1D11, S1R3C1_DP47_1H1, S1R3A1_CS_1B12, S1R3B1_ BMV_1H5, S1R3A1_DP47_1A6, S1R3B1_DP47_ 1E1 or S1R3B1_BMV_1A1.

17. The binding protein of claim 16, wherein the binding protein comprises:

- (a) a VH having the amino acid sequence that is at least 95% identical to any one of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 65 or 67; or
- (b) a VL having the amino acid sequence that is at least 95% identical to any one of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 63, 64, 66, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94 and 95; or
- (c) a VH of (a) and a VL of (b); or
- (d) a VH and a VL amino acid sequence that are at least 95% identical to the VH and VL, amino acid sequences, respectively, in any one of S1R2A_CS_1F7, S1R2A_CS_1D11, S1R2C_CS_1D3, S1R2C_CS_1H12, S1R2A_CS_1D3, S1R3B2_BMV_1E1, S1R3C1_CS_1D3, S1R3B2_DP47_1E8, S1R3B2_BMV_1G2, S1R3B2_BMV_1H5, S1R3C1_CS_1A6, S1R3B2_DP47_1C9, S1R3B2_DP47_1E10, S1R3C1_CS_1B10, S1R3A1_BMV_1F3, S1R3B1_BMV_1G11, S1R3A1_BMV_1G4, S1R3B1_BMV_1G11, S1R3A1_CS_1B9, S1R3B1_BMV_1H9, S1R3A1_CS_1B10, S1R3B1_BMV_1C12, S1R3C1_CS_1B10, S1R3B1_BMV_1C12, S1R3C1_BMV_1H11, S1R3B1_BMV_1C12, S1R3C1_BMV_1H11, S1R3B1_BMV_1A10, S1R3A1_CS_1D11, S1R3C1_DP47_1H1, S1R3A1_CS_1B12, S1R3B1_BMV_1A10, S1R3A1_CS_1D11, S1R3C1_DP47_1H1, S1R3A1_CS_1B12, S1R3B1_

BMV_1H5, S1R3A1_DP47_1A6, S1R3B1_DP47_ 1E1 or S1R3B1_BMV_1A1.

**18**. The binding protein of claim **16**, wherein the binding protein comprises:

- (a) a VH having the amino acid sequence of any one of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 65 or 67; or
- (b) a VL having the amino acid sequence of any one of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 63, 64, 66, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94 or 95; or
- (c) a VH of (a) and a VL of (b); or
- (d) a VH and a VL amino acid sequence of the VH and VL, amino acid sequences, respectively, in any one of S1R2A_CS_1F7, S1R2A_CS_1D11, S1R2C_CS_ 1D3, S1R2C_CS_1H12, S1R2A_CS_1D3, S1R3B2_ BMV_µl, S1R3C1_CS_1D3, S1R3B2_DP47_1E8, S1R3B2_BMV_1G2, S1R3B2_BMV_1H5, S1R3C1_CS_1A6, S1R3B2_DP47_1C9, S1R3B2_ DP47_1E10, S1R3C1_CS_1B10, S1R3A1_BMV_ 1F3, S1R3B1_BMV_1G11, S1R3A1_BMV_1G4, S1R3B1_BMV_1H11, S1R3A1_CS_1B9, S1R3B1_ BMV_1H9, S1R3A1_CS_1B10, S1R3B1_BMV_ 1C12, S1R3C1_BMV_1H11, S1R3B1_BMV_1A10, S1R3A1_CS_1D11, S1R3C1_DP47_1H1, S1R3A1_ CS_1B12, S1R3B1_BMV_1H5, S1R3A1_DP47_ 1A6, S1R3B1_DP47_1E1 or S1R3B1_BMV_1A1.

**19**. The binding protein of claim **14** or claim **16**, which is a SMIP.

**20**. A SMIP comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of any one of SEQ ID NOS: 159, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231 or 233, excluding the leader sequence.

**21**. The SMIP of claim **20**, comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of any one of SEQ ID NOS: 159, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231 or 233, excluding the leader sequence.

**22**. The SMIP of claim **20**, comprising the amino acid sequence of any one of SEQ ID NOS: 159, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231 or 233, excluding the leader sequence.

23. A nucleic acid molecule encoding the SMIP of claim 20.

**24**. A nucleic acid molecule that encodes a binding protein that specifically binds ErbB2, wherein the nucleic acid molecule comprises a nucleotide sequence selected from:

(a) the nucleotide sequence of any one of SEQ ID NOS: 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118,

120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154 or 156; or

(b) the nucleotide sequence of any one of SEQ ID NOS: 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155 or 157; or

(c) both the nucleotide sequence of (a) and the nucleotide sequence of (b).

**25**. The nucleic acid molecule of claim **24**, comprising the nucleotide sequence of any one of SEQ ID NOS: 158, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230 or 232.

26. A composition comprising the SMIP of claim 20.

27. The composition of claim 26, further comprising an additional therapeutic or diagnostic agent.

**28**. The composition of claim **27** that comprises an additional therapeutic agent, wherein the therapeutic agent is a chemotherapeutic or anti-inflammatory agent.

**29**. A host cell comprising a nucleic acid molecule of claim **24**.

**30**. The host cell of claim **29**, selected from the group consisting of an HEK cell, an NS0 cell and a CHO cell.

**31**. A method for producing a binding molecule that specifically binds ErbB2, or a SMIP that specifically binds ErbB2, comprising the step of culturing the host cell of claim **29** under conditions the permit protein expression.

**32.** A method for reducing ErbB2-mediated proliferation of a cancer cell comprising the step of administering to a subject or mammal in need thereof an effective amount of a composition of claim **26**.

**33**. A method for reducing tumor growth of an ErbB2expressing tumor, comprising administering to a subject or mammal in need thereof an effective amount a composition of claim **26**.

**34**. A method for increasing apoptosis in an ErbB2-expressing tumor, comprising administering to a subject or mammal in need thereof an effective amount of a composition of claim **26**.

**35**. The binding protein of claim **1**, which is detectably labeled.

**36**. A method for detecting an ErbB2 expressing tumor in a subject, comprising administering the binding protein of claim **35**.

**37**. A method for detecting ErbB2 in a sample from a subject comprising the step of contacting the sample with a binding protein of claim **14** or **16**, or a SMIP of claim **20** under conditions that permit binding and detecting binding, wherein binding indicates the presence of ErbB2.

**38**. A method of treating cancer characterized by ErbB2 expression comprising administering to a mammal or subject in need thereof an effective amount of a binding protein of claim **1**.

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